A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy

A dissertation submitted in partial fulfilment of the requirement of The Tamil Nadu Dr. M. G. R. Medical University For the M.S. Branch-I (General Surgery) Examination to be held in April 2

DECLARATION CERTIFICATE

This is to declare that the dissertation titled “Effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy” in the department of general surgery is my own work, done under the guidance of Dr. Mark Ranjan Jesudason, Professor and Head, Colorectal Surgery, submitted in partial fulfillment of the rules and regulations for the M.S Branch I – General Surgery degree examination of The Tamil Nadu Dr. M.G.R Medical university, Chennai, to be held in April 2017.

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BONAFIDE CERTIFICATE

This is to certify that “Effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy” is a bonafide work of Dr. Farheen Khan, in partial fulfillment of the requirements for the M.S. General Surgery examination (Branch I) of The Tamil Nadu DR M.G.R. Medical University to be held in April 2017.

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ORIGINALITY CERTIFICATE

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Introduction

Rectal cancer is third most common cancer worldwide. Every year more than a million cases are diagnosed worldwide. The male gender predilection is more than female gender. The mortality and morbidity associated with the disease and the intervention is still high. It is the third most common cause of cancer related deaths in the world. (1), (2). The surveillance epidemiology and end results database (SEER) registries worldwide report survival data from different areas and regions. In India, the registries report highest incidence of rectal cancers in men from Kerala and Bangalore whereas for women the cancer incidence is high from Nagaland and Aizwal.

Rectal cancer presents commonly as bleeding per rectum or intestinal obstruction. Evaluation of bleeding per rectum especially in males over 60 years of age should be done thoroughly. Clinical examination would include an outpatient proctoscopy and digital rectal examination. Local causes of bleeding per rectum have to be ruled out like hemorrhoids and fissure in ano. A full anemia workup is contributory. These cancers can present as anemia of chronic disease. A rigid or flexible sigmoidoscopy as an outpatient is readily available and has high diagnostic value. For completion a colonoscopy after good colonic preparation is done to rule out synchronous lesions.

Mucosal biopsy are taken. For evaluation of metastatic workup and staging an MRI pelvis is very helpful and is the standard tool. Chest X ray is done to rule out metastatic lesions in the chest.

Once diagnosis is made a multidisciplinary approach is required for further management. Patients presenting with acute intestinal obstruction require a diversion or resection followed by definitive therapy. Staging of cancers is done using AJCC TNM staging, where T is the depth of tumor, N is the nodes and M is the distant metastases. Oncologic principles of surgery include complete resection of the tumor with adequate margins and clearance of lymphatics draining the tumor. To achieve the oncologic clearance the tumor is often down staged with neoadjuvant radiotherapy and concurrent chemotherapy. Neoadjuvant radio chemotherapy can be given a long course or short course chemotherapy. Currently IMRT is also being used to give focused three dimensional radiation to the tumor alone with little adverse effects on the surrounding tissues. Concurrent chemotherapy includes one or two cycles of 5 fluorouracil. Adjuvant therapy includes chemotherapy post operatively. Adjuvant therapy is usually adviced in stage II, high risk stage II and stage III disease. (3), (4), (5).

Investigators have suggested better long term survival in patients who receive adjuvant chemotherapy within a time frame post operatively. Overall, patients who

receive adjuvant chemotherapy following rectal cancer resection have better survival than those who fail to receive adjuvant therapy (3).

Few studies have impressed on the fact that time period to receiving first dose of adjuvant chemotherapy is critical and determines the disease free survival in the long term. A meta- analysis found poorer outcomes if chemotherapy is administered 8 weeks or more after surgery (6). If adjuvant chemotherapy is given beyond 12 weeks of surgical resection there is a decrease in survival as noticed by few studies (7) (8).

A meta-analysis has concluded that there is decrease in survival of 14% for each 4 week delay in administration of adjuvant chemotherapy (9).

Multiple factors are associated with postoperative course and outcome in rectal cancer. High morbidity associated with postoperative complications like wound dehiscence and urinary incontinence have resulted sometimes in failure of receiving adjuvant chemotherapy rather than delay in initiation (10). Postoperative complications like wound infection lead to delays in chemotherapy resulting in recurrences, poor overall outcomes. These complications correlate significantly with delay in commencement of chemotherapy in an analysis in a recent study (11).

Several studies demonstrate that large proportions of patients do not receive adjuvant chemotherapy or and experience treatment delays (12). Literature has limited

information regarding the factors associated with increased delay to commencement of adjuvant therapy. We are yet to find optimal time frame for the commencement of adjuvant chemotherapy post curative rectal surgery. Hence this study.

Objective and aim of the study

Aim: The aim of this study is to the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and risk factors associated with delay in chemotherapy.

Objectives:

Primary: To compare the overall survival and disease progression free survival in Patients receiving chemotherapy within and beyond 8 weeks of curative resection of rectal cancer.

Secondary:

- To establish an optimal time frame that constitutes delay in adjuvant chemotherapy leading to worse outcomes.
- To assess the risk factors causing delay in receiving adjuvant chemotherapy

Summary of the research scheme

The proposed study is a historical cohort study to assess the survival and disease free survival in patients receiving chemotherapy before and after 8 weeks of curative rectal cancer surgery. All patients who underwent rectal cancer surgery in the Department of Colorectal surgery at Christian Medical College, Vellore from 1st January 2007 requiring adjuvant chemotherapy will be considered for inclusion in the study.

Patients with metastatic disease, R2 resection or not requiring chemotherapy will be excluded from the study.

Consecutive patients will be recruited till the study sample size of minimum 38 each exposed (received chemotherapy within 8 weeks of surgery) and unexposed (received chemotherapy after 8 weeks of surgery) subjects is reached. Data will be collected using a prospectively maintained database.

Follow up will be done from hospital records, telephonic interviews and postal proforma.

The patient demographics, clinical details and relevant investigation results will be entered in a pro forma designed for the purpose of this study. The data collected will be analyzed for survival using Kaplan Meier Curve and Cox proportionate Hazards model.

Risk factors for delay in chemotherapy will be analyzed using Chi square and Independent sample T test and logistic regression. The optimal cut-off for delay in chemotherapy will be calculated using receiver-operator characteristic (ROC) curve.

Literature review

Carcinoma rectum

History

The historical aspects of modern rectal cancer resection can be traced back to 1884. Czérny described the first abdomino perineal resection (APR). In 1885, Kraske excelled in the understanding of trans sacral approach of rectal resection and anastomosis. In 1908, Miles improved on the APR by emphasizing the need of doing a wide perineal excision. He practised removal of rectum with a high ligation of the superior hemorrhoidal artery as well as excision of the attachments of the of the rectum to the abdomen and the iliac lymph nodes. Despite the improvements the mortality in Miles' first series exceeded 42%.

Over the next 80 years with the modifications in intra, pre and post operative care the mortality and complications with rectal cancer surgery changed and improved significantly. But there were no advancements in oncologic techniques during this period. Total mesorectal excision (TME) for carcinoma of the rectum was

popularised in the late 1980s by William Heald. The technique involved sharp dissection to perform the complete excision of the mesorectum and its associated lymphatics along the subtle fascial planes that encompass the rectum. To reduce the local recurrence, the zone of downward spread within the mesorectum was described. Recently, local excision is being combined with neoadjuvant and adjuvant chemoradiotherapy to maximize local control with a minimally invasive approach.

Epidemiology

Over hundred thousand new cases of colorectal cancer were diagnosed globally in 2002. The incidence of colorectal cancer and related death is common. There is a correlation of increasing trend of incidence of rectal cancer with increasing age. Most cases are seen in patients over 60 years of age. Among male population it is third common and is second common cancer among female population (13).

Developed countries are more commonly affected, upto around 60% cases are reported from developed countries. The number of rectal cancer related deaths account for 8% of cancer deaths worldwide. Overall, colorectal cancer is the fourth

most common cause cancer related mortality.

In India, the annual incidence rates for rectal cancer in men are 4.1 per 100000.

In women, rectal cancer has low incidence rates as compared with colon cancer (14).

In India highest incidence of colorectal cancer in men is from Trivandrum followed by Bangalore and Mumbai. Nagaland and Aizwal has high incidence of colorectal cancer in women (14).

Etiology and syndromic association

Geographical variation:

There is global variation of incidence rates of rectal cancers in the world. The highest incidence is noted in developed countries whereas low incidence is from developing countries. But noticed is a trend from developed to developing countries as migrants with rectal and colon cancers move from low incident areas to high incident areas and mix with high risk population. Over the last 50 years there is significant increase in the risk of development of colorectal cancer in the low risk countries and this can be attributed to the changes in lifestyle, diet and migration to high risk areas.

Dietary factors:

According to The European Prospective Investigation into Cancer (EPIC) and Nutrition study there is significant relationship between diet, lifestyle, genetic and environmental factors. There is association between rectal cancer and increasing processed meat. Fish and dietary fiber was found to be protective. EPIC has also concluded that fruit and vegetable intake can be protective. Low dietary fiber is associated with increased risk of rectal cancer.

Lifestyle:

Alcohol consumption of 30-45g/day increases risk of development of colorectal cancer by 16%. Consumption more than 45g/day increases the risk by 41% (15). Obesity increases risk of colorectal cancer (16). Tobacco smoking negates the benefits of anti oxidation by fruits and vegetables, but there is no definite conclusion that smoking increases the risk of rectal cancer (17).

Other factors:

- Ulcerative colitis has been known to be associated with increased risk of

developing colorectal cancer. It is associated with the time duration from the onset of the disease and duration of active colitis. Earlier the onset of duration of disease higher is the chance of malignant transformation (18).

- Immunosuppression post organ transplantation, long term steroid intake (19) (20)

- Diabetes mellitus associated with insulin resistance: Studies have shown an association of insulin-like growth factors with the development of colorectal cancers (19).

- Use of anti inflammatory like non steroidal analgesics and hormone replacement therapy is associated with decreased risk of colorectal cancer.

- Uretero colic anastomosis is known to have high risk of development of colorectal cancer due to chronic irritation of the mucosa with urine.

Hereditary colorectal cancer:

30% of colorectal cancer carry risk of familial penetrance hereditary syndromes.

Common syndromic associations are with

- Familial Adenomatous Polyposis
- Attenuated Familial Adenomatous Polyposis
- MYH associated polyposis (21)
- Lynch syndrome (22) (23)
- Juvenile Polyposis
- Peutz Jeghers syndrome

Familial Adenomatous Polyposis is an autosomal dominant condition which is identified by presence of more than hundred adenomatous polyps in the large bowel. The association of colorectal cancer in FAP is almost 100% in third to fifth decade of life. The germline mutationof adenomatosis polyposis coli tumor suppressor gene is located on chromosome 5q21 causes majority of familial adenomatous polyposis. (24) (25).

Lynch Syndrome is an autosomal dominant condition which is characterized by microsatellite instability. It is associated with increased risk of urinary tract, ovary, pancreatico biliary and brain tumors. It was formely known as Hereditary Non Polyposis Colon cancer. Microsatellite instability are defective DNA mismatch repair

Proteins. These patients are at an increased risk of metachronous and synchronous lesions.

Various colorectal cancer associations which have conflicting evidence in the Literature (26)

- Ischemic heart disease
- Decreased vegetable and fruit intake
- History of radiation therapy for any other pelvic organ malignancy
- Immunodeficiency conditions – primary or genetic
- history of treatment for lymphoma
- Decreased physical activity resulting in obesity

Anatomy of rectum

The rectum is anatomically located in the pelvis. At the sacral promontory it continues as the rectum from the recto sigmoid junction and ends at the anorectal junction. The longitudinal muscle layer of the rectum is a continuation of the tenia coli at the sigmoid colon. The rectum has three lateral curvatures: the upper and lower are convex to the right, and the middle is convex to the left. Inside the lumen these curvatures are called Houston's valves.

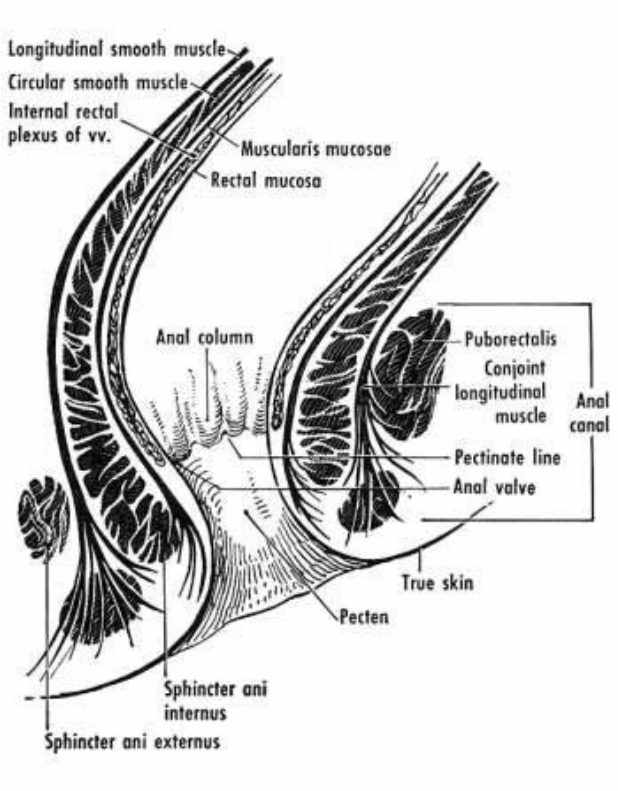


Figure 1 Anatomy of rectum

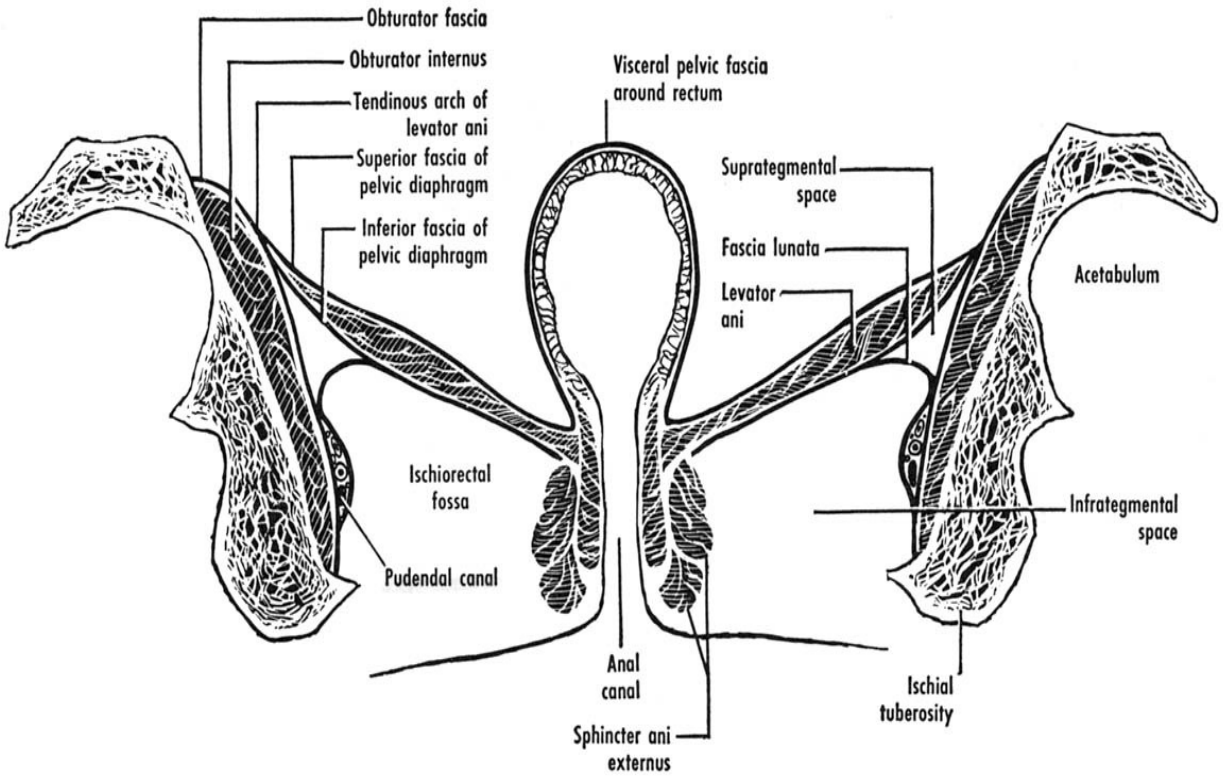


Figure 2 Anatomy of pelvis

The adult rectum is approximately 12–18 cm in length.

- Parts of rectum: Upper third - mobile and has a peritoneal covering anteriorly and laterally
- Middle third - peritoneum covers the anterior and part of the lateral surfaces
- Lowest third - Lies deep in the pelvis and is surrounded by fatty mesorectum and

fascial layers (Denonvilliers' fascia, Waldeyer's fascia). These fascial layers are a barrier to malignant invasion and form the basis of total mesorectal resection and circumferential resection margin.

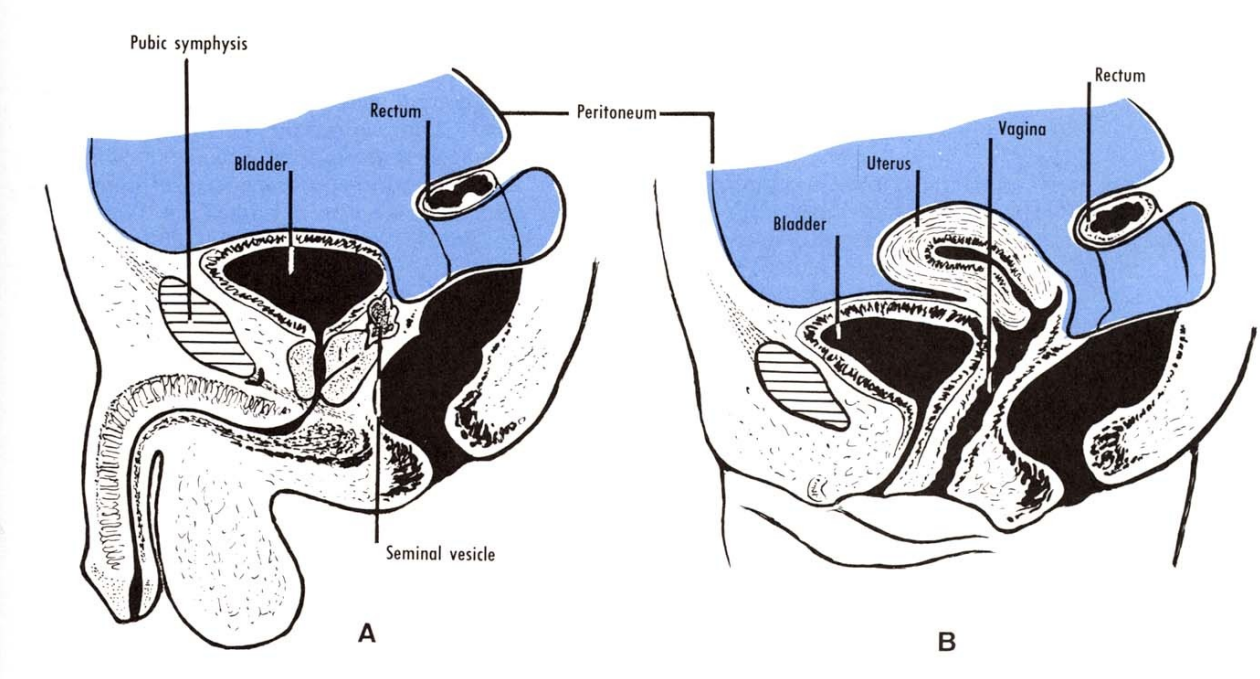


Figure 3 Difference in A. male and B. female pelvic anatomy

Blood supply:

The inferior mesenteric artery continues as the superior rectal artery and supplies the rectum and the anal canal. Middle and inferior rectal arteries also share the supply. Venous drainage is by superior hemorrhoidal veins which drain to join the inferior

mesenteric vein. Inferior mesenteric veins joins the portosystemic circulation into the splenic vein.

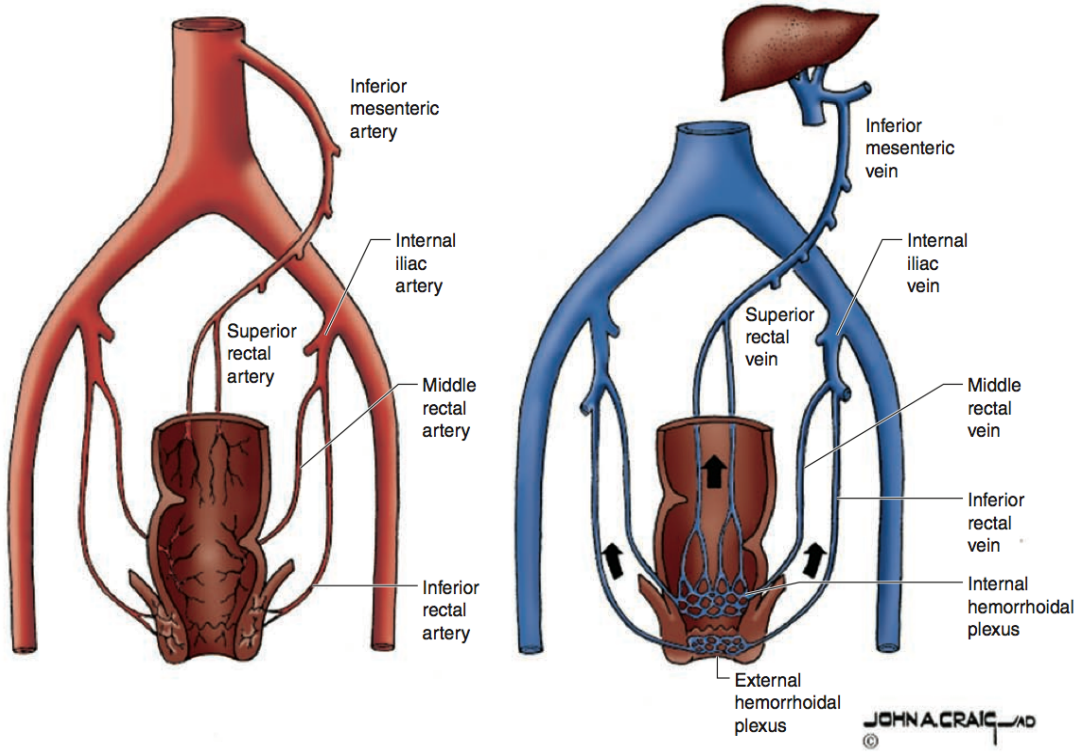


Figure 4 Vasculature of rectum and anal canal

Lymphatic Drainage:

The rectal mucosa has an extensive network of lymph drainage that forms a network With muscular layers. The lymphatic drainage flows upwards. Lymph drains laterally also in the downward direction. The flow of lymph dictates the clearance of nodes and requires a high proximal clearance of nodes in rectal resection. Pelvic side walls

develop lymphatic metastases when the upward direction of the lymph flow is obstructed either mechanically by the tumor or due to the emboli.

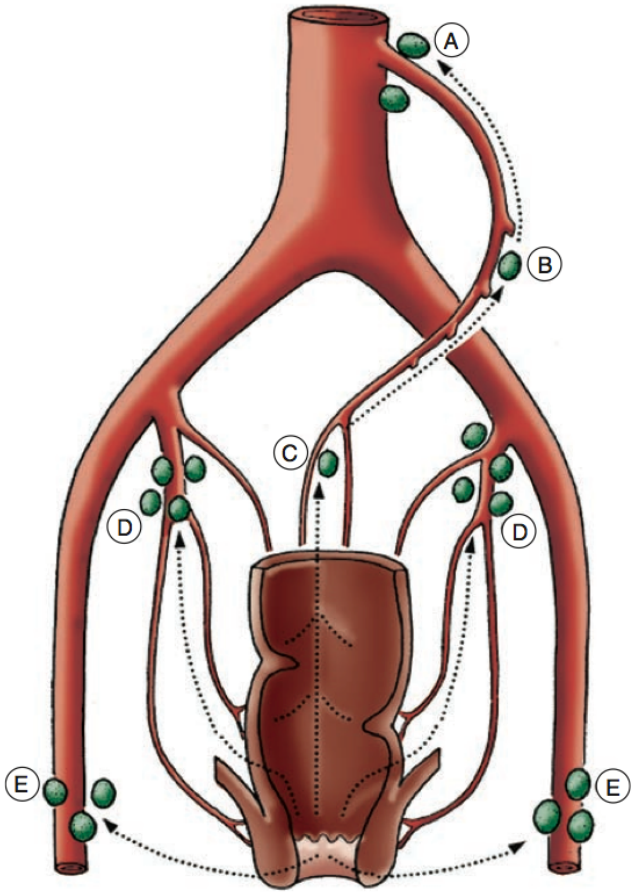


Figure 5 Lymphatic flow of the rectum with nodal station, A – level of inferior mesenteric vessels, B – Origin of sigmoid colon, C – Presacral nodes, D and E – Internal iliac and inguinal nodes

Innervation:

Parasympathetic fibers supply the smooth muscle, including the internal sphincter.

Sympathetic fibers are mainly vasomotor. Somatic motor fibers supply the external

sphincter. Sensory fibers are concerned with the reflex control of the sphincters and

with pain.

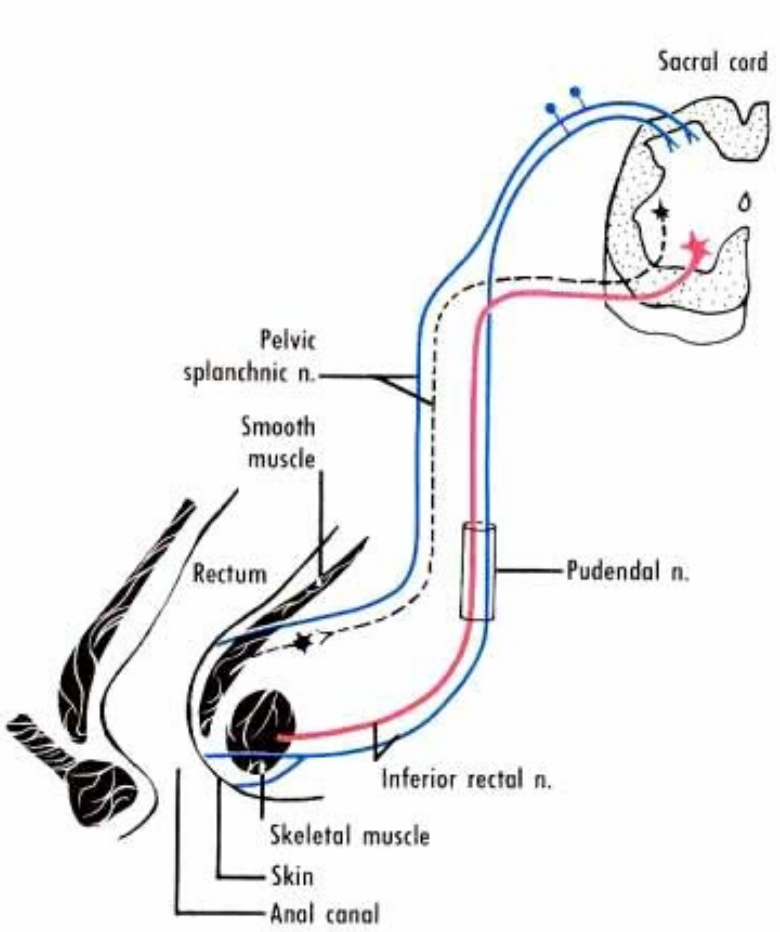


Figure 6 Nervous supply of rectum and anal canal

Staging of rectal cancer

Staging of cancer serves the purpose to describe the anatomic extent of the lesion. Staging is done by clinical examination, radiology, and pathology. Staging facilitates planning treatment, tumor response to treatment. Staging also aids in comparing the results of different types of treatment regimens, and in prognosticating. Dukes' and TNM staging systems are the commonly used staging tools in colorectal cancers. Presently, the highly accepted staging system for rectal cancer worldwide is TNM classification system.

In 1987, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUC) introduced the TNM staging system for colorectal cancer. This system was updated in 2010. The TNM staging system is based on tumor invasion, lymph nodal involvement and distant metastases.

Cuthbert Dukes' published his staging system in 1932 based on cases managed at St. Mark's Hospital London. He classified tumors by pathological local tumor invasion into

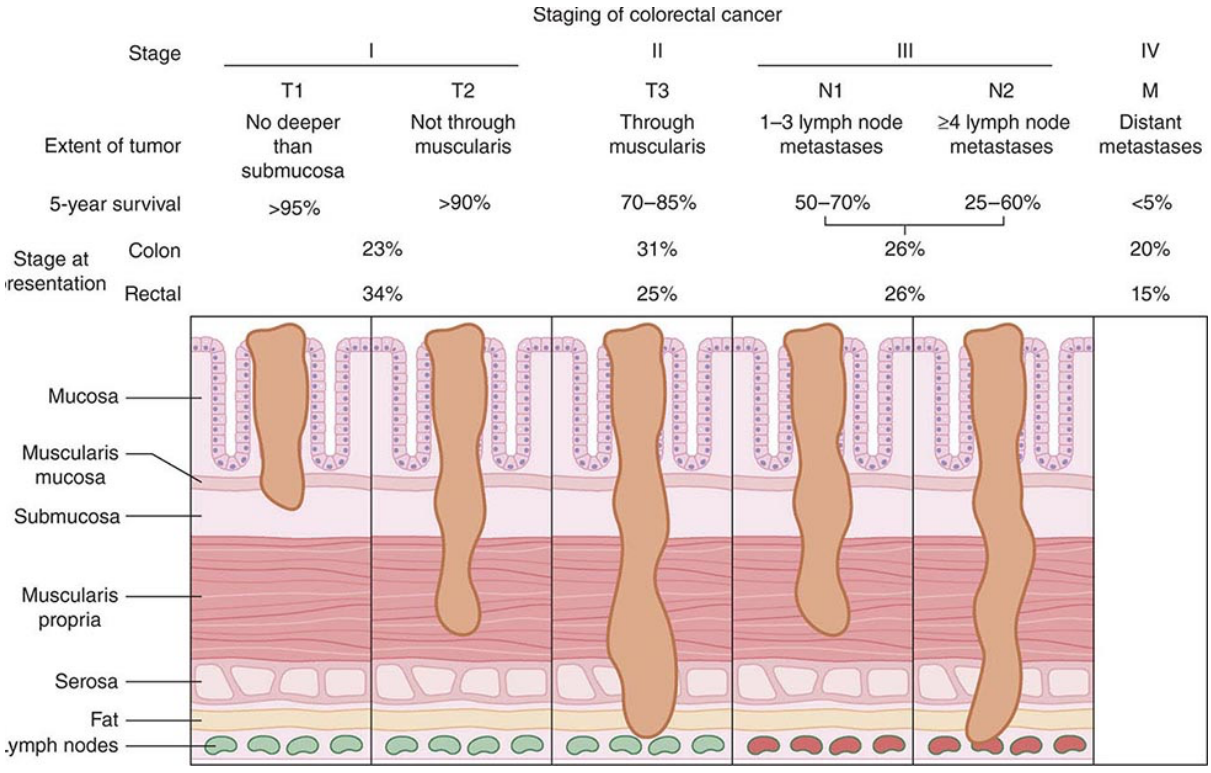
A – Confined to rectal wall

B – Breached extra rectal tissue

C – Presence of lymphnodal metastases

D – Distant metastases

Figure 7 TNM staging of rectal cancer and associated survival



Primary Tumor (T)

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- **T1** Tumor invades submucosa
- **T2** Tumor invades muscularis propria
- **T3** Tumor invades through the muscularis propria into pericolorectal tissues
- **T4a** Tumor penetrates to the surface of the visceral peritoneum[2]
- **T4b** Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in 1–3 regional lymph nodes
- **N1a** Metastasis in one regional lymph node
- **N1b** Metastasis in 2–3 regional lymph nodes
- **N1c** Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N2** Metastasis in 4 or more regional lymph nodes
- **N2a** Metastasis in 4–6 regional lymph nodes
- **N2b** Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- **M1b** Metastases in more than one organ/site or the peritoneum

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).
* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Figure 8 Detailed AJCC 7 TNM staging of colorectal cancer

Principles of treatment of rectal cancer

Operative management in rectal is of prime importance when it comes to curative therapy for rectal cancers. Surgery is based on two principle factors: complete resectionof tumor and lymphatic clearance. After a curative rectal cancer resection 5 years survival is found to be reasonable good depending on the extent of the disease at the time of diagnosis.

Management of rectal cancer has evolved over decades with advances in technology. Multidisciplinary discussions are required to plan patient management depending on the evaluation and after establishing the diagnosis (27). Staging of the disease is important and this requires an MRI of the pelvis. Imaging along with other investigations help in staging the disease.

Stage of the disease decides on surgical resection or preoperative Chemo radiotherapy. For patients with stage II and III rectal cancer combined preoperative chemo radiotherapy is recommended.

Neoadjuvant therapy

There are a number of potential advantages for using neoadjuvant chemoradiation. Radiation therapy sensitises the tissues and better action of chemotherapeutic agents. With combined chemoradiation higher doses of chemotherapy are delivered. Neoadjuvant chemotherapy potentially dowstages the disease to achieve a pathologic complete response in 15–30% of patients. Downstaging the tumor facilitates higher chance of negative resection margins. Also it aids in planning a sphincter- preserving operation. Other advantages of neoadjuvant chemoradiation includes preventing development of radiation enteritis. Pre operative radiation prevents radiation of anastomosis and small bowel radiation in the pelvis. Since the neoadjuvant chemoraditaion is before the operation compliance among patients is better. There are trials which show that preoperative radiotherapy followed by total mesorectal resection results in decreased risk of recurrence when compared with only operation. Dutch Colorectal Cancer Group demonstrated 8% risk of recurrence in patients who underwent only resection and no neoadjuvant radiation (28). Swedish

trial demonstrated benefit of survival in subjects receiving preoperative radiation as compared with surgery alone (48%) (29). The Swedish trial also demonstrated 27% recurrence in the surgery-alone group. Studies have concluded that preoperative radiation therapy plus surgery compared with surgery alone significantly reduced the 5-year overall mortality rate, cancer related mortality rate, and local recurrence rate (30).

The benefit of radiation in rectal cancer as a neoadjuvant therapy are:

- The local recurrence of tumor decreases post curative resection
- With concurrent chemotherapy radiation treats the locally advanced disease to downstage the diease for future resection
- To convert an abdomino perineal excision which requires a permanent stoma to a sphincter preserving surgery like low anterior resection
- Palliation of pain, bleeding and perineal discharge. Obstructive and diarrheal symptoms do not respond to local radiation and require surgical intervention like a bypass colostomy if disease is not resectable.

Evidence on reduction of local recurrence of disease after radiation is very strong and

it is strongly recommended for locally advanced disease which is not amenable to resection with adequate margins. Few meta analysis have documented the superiority of pre operative radiotherapy to adjuvant radiation.

Radiation can be administered in many ways. Conventionally, long course chemoradiation is given as a total dose of 45 -50.4 Gy in daily divided fractions (20 – 25 fractions). Concurrent chemotherapy, one or two cycles are administered along.

In Europe, short course chemotherapy is popular and is given as 25Gy in 5 fractions. This is followed by surgery.

Goals of rectal cancer surgery

The surgical resection aims at complete resection of the tumor with adequate margins and complete clearance of the draining lymphnodes. The goals include

Excision of mesorectal tissue and the locoregional blood supply.

Sphincter sparing surgery and reestablishment of bowel continuity at the time of surgery has become routine. Despite trial of maintaining bowel continuity

some patients might end up having a permanent stoma and hence should be explained pre operatively regarding the same.

The bony confines of the pelvis and close planes with urinary bladder, prostate and seminal vesicles limit dissection of the distal part of the rectum. In women the limitation is due to the proximity of vagina in the pelvis. The local recurrence, cure, mortality, anastomotic leaks, and colostomy rates after rectal cancer resections are related to surgical techniques.

Resection margin

- **Distal margin**

Rectal tumor are at 15cms or less from the anal verge on clinical scopy. These cancers are divided into upper, mid and lower rectal tumors based on the distance of tumor from the anal sphincter.

Upper rectal tumors: Less than 6cms from the anal verge

Mid rectal tumors: 6 -10cm from the anal verge

Lower rectal tumors: 11 -15cms from the anal verge

Anterior resections are performed for upper and mid rectal tumors whereas abdominoperineal resection is done for low rectal tumors. The choice of operative procedure performed ultimately depends onpatient and tumor characteristics. There is inconclusive evidence regarding the adequate distal resection margin for rectal cancer and it is still controversial. Rectal cancer spread upwards along the vascular pedicle and laterally. 5cms distal margin is traditionally accepted, although margin of 1 cm doesnot translate to higher rates of recurrence (31) (32) (33). Within the lumen tumor spreads to within 2cm unless it is a poorly differentiated tumor or is an aggressive tumor with systemic metástases. The National Surgical Adjuvant Breast and Bowel Project highlighted the fact that there was no significant differences in survival or local recurrence on comparing distal rectal margins of less than 2, 2–2.9, and greater than 3 cm. Hence a 2-cm distal margin is acceptable for resection of rectal carcinoma. A 5-cm proximal margin is still recommended (34).

- **Radial margin**

The importance of obtaining a negative circumferential or radial margin has

been impressed on in the last decade. The circumferential radial margin (CRM) is important than the proximal or distal margin for locoregional disease recurrence. Positive circumferential margin is an independent predictor of both local recurrence and survival. The Norwegian Rectal Cancer group reported on circumferential resection margins with 29-month median follow-up in 686 patients who had curative intent LAR with TME alone (no adjuvant radiotherapy) for rectal adenocarcinoma. The Norwegian group found that the overall local recurrence rate was 7% (22% with positive CRM and 5% with a negative CRM). 40% of patients with a positive CRM developed distant metastases whereas only 12% of those with negative CRM developed distant disease (35). In this study a positive CRM clearly affected survival. In another report of 90 patients undergoing resection for rectal cancer, when the radial margins were histologically positive, the hazard ratio (HR) for local recurrence was 12.2, and the HR for death was 3.2 when compared with those with clear circumferential margins.

Negative circumferential margin means radial margin of the tumor is atleast 1mm

away from the normal tissue.

Operative technique is of paramount importance in the management of rectal cancer resection. Following oncologic principles describes the types of resections performed for rectal tumors.

Total mesorectal excision

Total mesorectal excision was popularized by Heald and involves dissection in between the mesorectum and parietal fascia. The dissection is carried out in between an avascular plane where there is loose areolar tissue. Rates of tumor recurrence with total mesorectal excision have been reported as 4 % (36). There is better post operative bowel function and anastomotic leak rates are low as compared to other surgical techniques. The two popular trial for total mesorectal resection are Swedish Trial and the Dutch Trial for standardisation of total mesorectal resection. The Dutch trial concluded a recurrence rate of 8.2% with surgery alone.

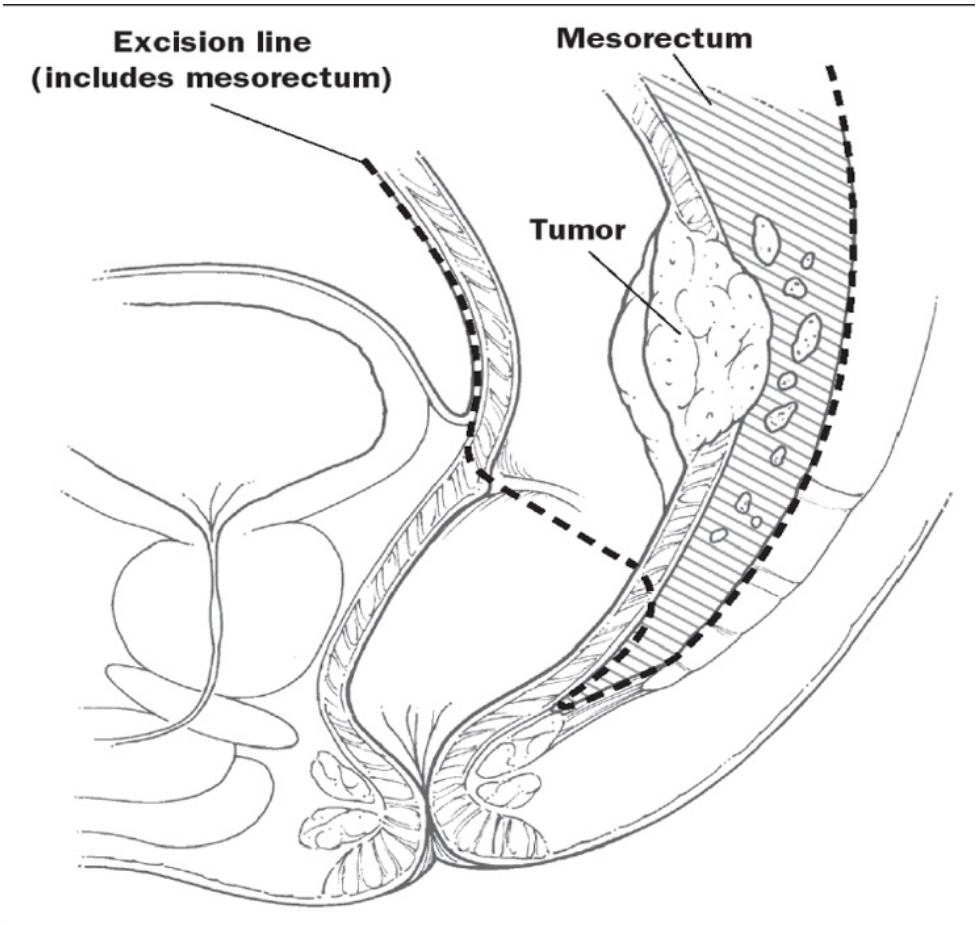


Figure 9 Total Mesorectal Resection

Strategies for low rectal cancers

The operative procedure employed for low rectal cancers is influenced by the tumor relation with the pelvic floor and the distance from the anal sphincter. The choices of

procedure are as following although in such cases also sphincter preserving surgery is tried with neoadjuvant therapy.

- Low anterior resection
- Ultra low anterior resection
- Abdominoperineal resection

Low and ultra low anterior resections successfully restore the intestinal continuity by doing a stapled coloanal anastomosis or a J shaped colonic pouch prior to anastomosis. It is preferable to avoid using the sigmoid colon as the proximal component of a coloanal anastomosis, because the blood supply to the sigmoid from the Inferior mesenteric artery may be precarious, and the presence of diverticular disease, common in the sigmoid colon, is often considered to be a risk factor for anastomotic leak. Anastomotic leak rates depend on the patient factors and tumor characteristics. Also it depends on the site of the anastomosis. The leak rates based on site of coloanal/ colorectal anastomosis are as follows (37).

- Above the peritoneal reflection – 1.5%

- Below the peritoneal reflection – 6.6%

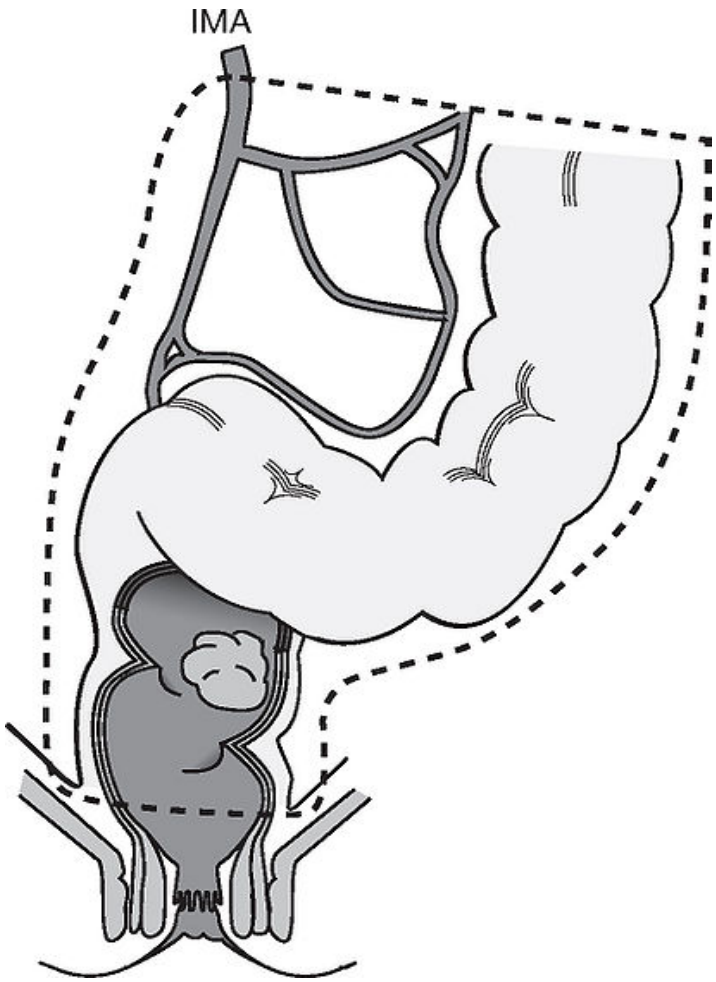


Figure 10 Low anterior resection

Hartmann's procedure

Inpatients presenting with obstruction/ bleeding in acute settings like perforation peritonitis, an emergency procedure is done. Most commonly for rectal cancers or low sigmoid malignancy a Hartmann's procedure is performed. Hartmann's procedure

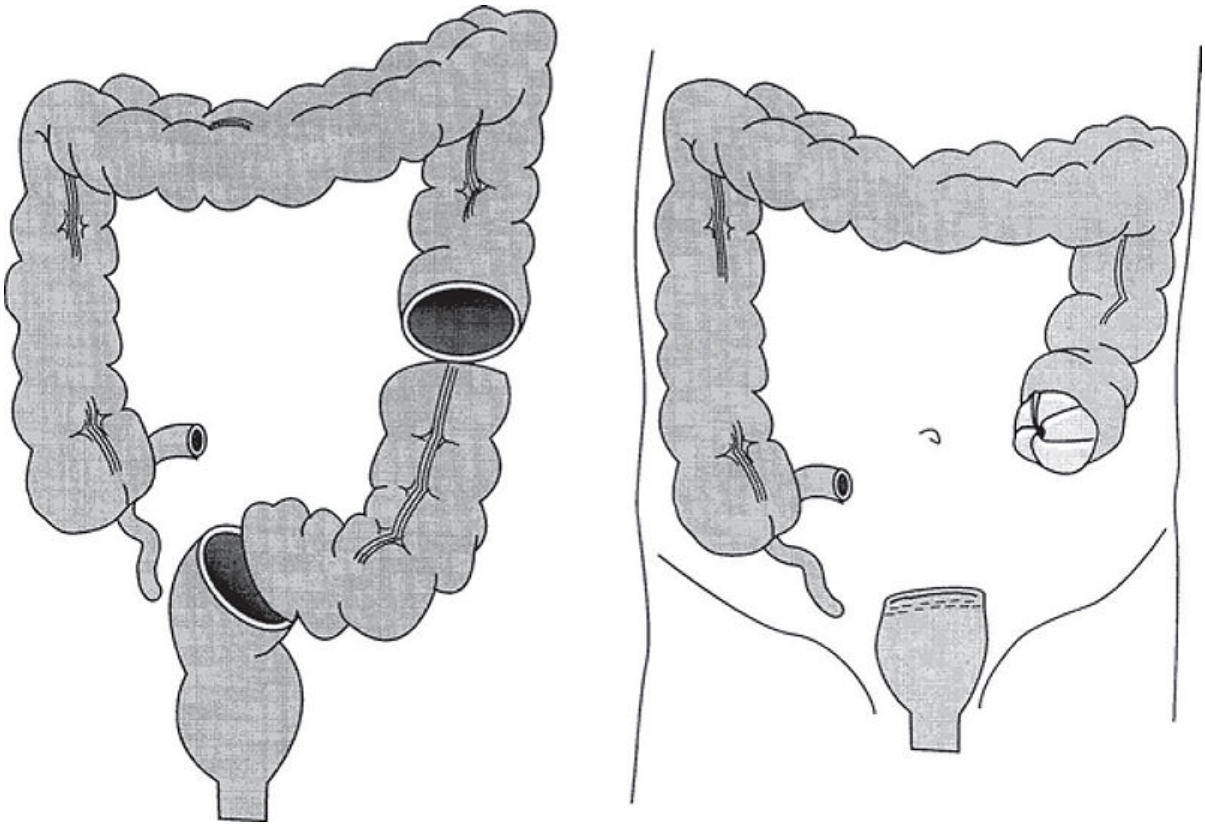


Figure 11 Hartmann's procedure

involves removal of the tumor and closure of the distal rectal stump and a proximal stoma. In advanced diseases where resection margin are not achieved are associated with high morbidity, leak rates and mortality. Reversal can be done at a later date but majority of the patients end up with a permanent stoma.

Abdominoperineal resection

Abdominoperineal resection is known as the Miles operation. The distal rectal cancers which are too low to perform an anastomosis have been treated with an abdominoperineal resection. The rectum is dissected in the same plane as total mesorectal excision down till the pelvic floor. The sigmoid colon is brought out as end colostomy. Types of abdominoperineal resections:

- Conventional abdominoperineal resection
- Radical abdominoperineal resection

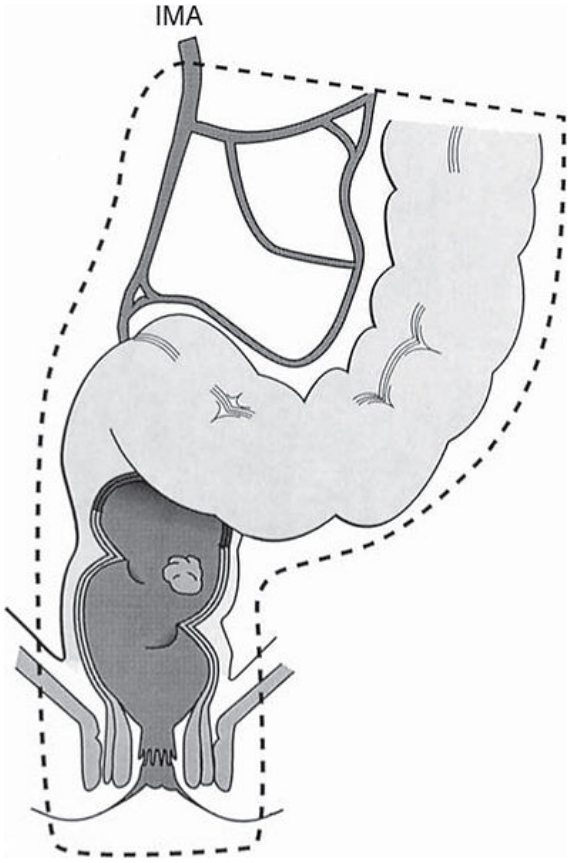


Figure 12 Abdominoperineal resection

The difference between the above two types of abdominoperineal resection is the extended perineal resection in the radical approach which leads to decreased rates of positive circumferential resection margins.

The APR is associated with significant morbidity and mortality (0 to 6.3%). Urinary incontinence, impotence, premature ejaculation, perineal wound infections are associated morbidities. Significant long-term morbidity is associated with permanent colostomy. Despite radical resection, 20% recur locally.

Recurrence rates depend on location of the tumor within the rectum, the surgical

Technique used, and the adjuvant therapy. For patients with cancers that involve the sphincter apparatus or for those who are incontinent of feces, an APR is performed to remove the rectal specimen.

Adjuvant chemotherapy

The goals of administration of the adjuvant therapy is to reduce recurrence or relapse of disease. Locoregional disease control and survival was better in patients who receive adjuvant chemotherapy (38). This statement holds true in stages II and III. The National Surgical Adjuvant Breast and Bowel Project C-04) trial demonstrated better efficacy and better 5 year survival in patients with stage II and III disease that single agent use of 5-fluorouracil (5-FU) and leucovorin treatment had a significantly better when compared with 5-FU and levamisole (74 vs 69%) (39). 5 FU reduces the relative risk of death in resectable rectal cancers. Adjuvant chemotherapy should be offered to high risk stage II and stage III disease (40)

Two major studies conducted which showed siginificant reduction in rates of

recurrence in rectal cancers in patients who receive adjuvant therapy are:

- The North Central Cancer Treatment Group trial
- The Eastern Cooperative Oncology Group trial

Duration of initiation of the adjuvant chemotherapy has been a topic of study for several decades. Studies have found that there is no benefit of administering adjuvant chemotherapy after 6 to 8 months of rectal cancer resection as there is no survival benefit. Few studies have demonstrated that receiving adjuvant chemotherapy after 8 weeks of operation is associated with significant reduction in overall survival rates. The delay in chemotherapy was usually noted in elderly unmarried men, also in patients with post operative prolonged hospital stay due to anastomotic leaks and wound infection (41).

The common chemotherapeutic agents used are 5 Fluorouracil, Oxaliplatin and Irinotecan (42).

In few countries monoclonal antinbodies like Bevacizumab and Cetuximab are being

tries. These monoclonal antibodies target the Vascular endothelial growth factors and the Epidermal growth factors. Till date adjuvant therapy with biological agents have not shown promising results (43).

Structured abstract

Background:

Colorectal cancer is the third most common cancer worldwide. Adjuvant chemotherapy is recommended in patients withhigh risk stage II and III cancers. Studies have demonstrated that time to first chemotherapy after rectal resection affects the overall outcome in terms of survival and disease free state. This has however not been proven conclusively. There are multiple factors associated with delay in adjuvant chemotherapy.

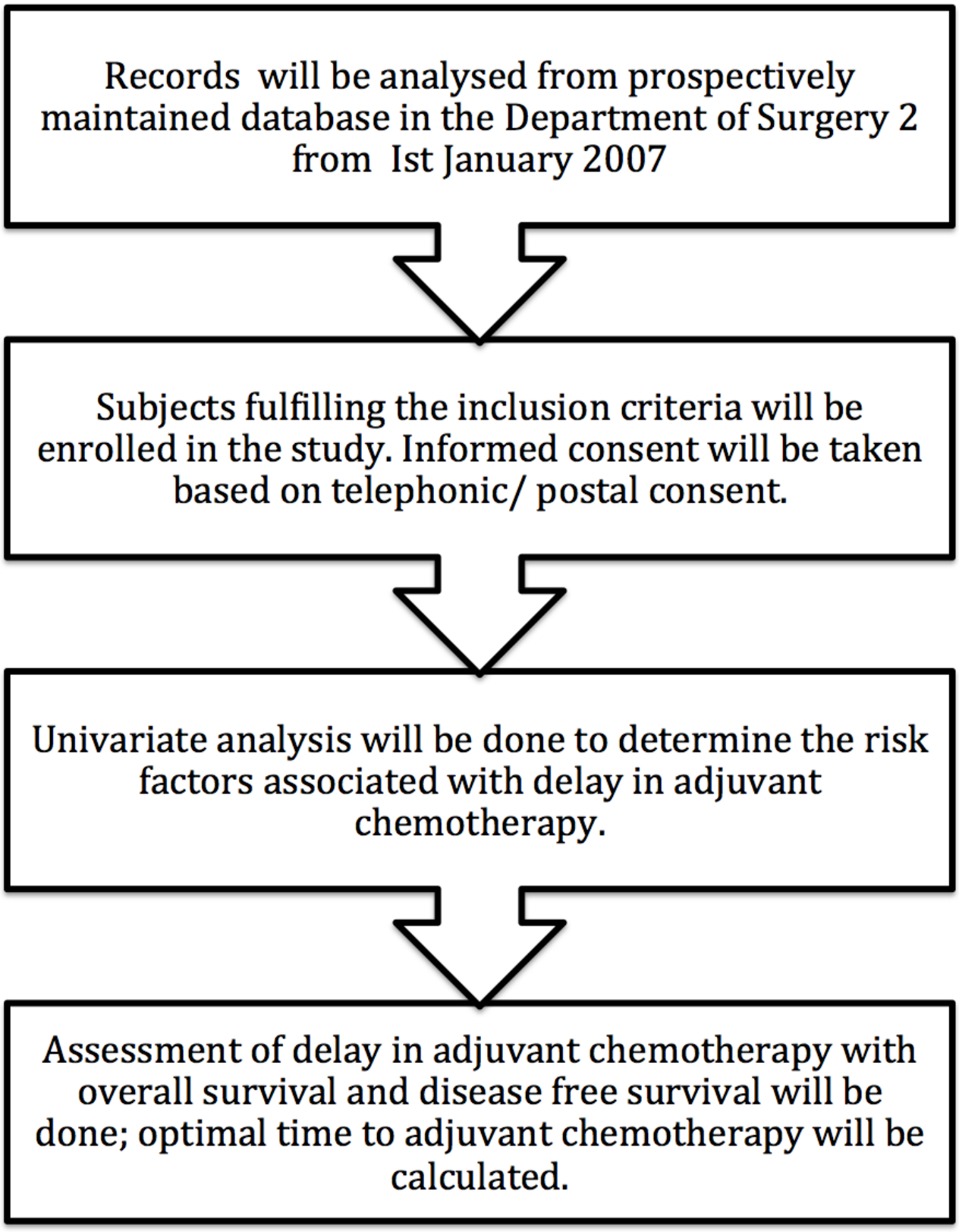
Aim: This study is aimed at assessing overall and five year survival in patients who receive chemotherapy withina and after 8 weeks of curative rectal cancer resection and to assess the factors causing delay in receiving chemotherapy.

Setting and design: This is a historical bidirectional cohort study in patients after curative rectal cancer surgery in the Department of Surgery 2 at Christian Medical College , Vellore.

Materials and methods: Consecutive patients who underwent curative rectal cancer

surgery in the Department of Surgery 2 at Christian Medical College Vellore from 1st January 2007 and requiring adjuvant chemotherapy will be included. The data collected will be collected on the pro formas and through telephonic conversations. Data will be analyzed for survival using Kaplan Meier Curve and Cox proportionate Hazard model. Risk factors for delay in chemotherapy will be analyzed using Chi square and Independent sample T test and logistic regression. The optimal cut-off for delay in chemotherapy will be calculated using a receiver-operator characteristic (ROC) curve.

Detailed algorithm of the study



Methodology

Study setting:

This Study was carried out in department of colorectal surgery in Christian medical college, Vellore.

Christian Medical College

Christian medical college, Vellore is a 2695 bedded multispeciality hospital and medical college which caters to 1.9 million out patients and 1.2 lakh in- patients per year. It caters to 5500 outpatients, 2500 in patients, 22 clinics and 30 births on a daily basis. The speciality of colorectal surgery has traditionally remained under the general surgery department in most places of India and so also in Christian Medical College, Vellore. A separate colorectal unit was formed in 2003, but it still functions as one of the units (surgery unit 2) of the department of general surgery. The spectrum of diseases managed by the colorectal speciality surgical unit include colo-rectal cancers, inflammatory bowel disease, pelvic floor disorders, rectal prolapse and complex anal, rectal and entero-cutaneous fistulae.

There are 1200-1400 admissions on a yearly basis and the number of surgeries performed amounts to a total of 1400 approximately with 40% of the surgeries being speciality (colorectal) surgeries. The most commonly performed surgeries are right hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection, low anterior resection and abdominoperineal excision.

I. Setting and locations – Department of General surgery 2

Period of recruitment – 01 January 2007 till sample size is achieved

Data collection – Will be done by the principal investigator in the Department of General surgery 2

Follow-up – Patients will be followed-up until last hospital visit and thereafter via telephonic conversation/ postal pro formas.

II**. Participants:**

Sample selection, with the inclusion and exclusion criteria

Inclusion criteria:

i. All individuals who underwent rectal cancer resection and required adjuvant

chemotherapy (T3 with high risk features, T4, N1 disease)

ii. R0 resection (all gross disease resected by en bloc resection with margins histologically free of disease) or R1 resection (all gross disease resected by en bloc resection with margins histologically positive for disease)

Exclusion criteria:

i.Individuals with metastatic disease

ii. Patients who did not receive chemotherapy

iii.Individuals with R2 resection (residual gross disease remains unresected)

III. Sampling strategy:

A consecutive sampling strategy will be employed for this study, wherein all patients who underwent rectal cancer resection under Department of Colorectal Surgery at CMC Vellore will be considered for enrollment in the study

IV. **Variables:** Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

V. **Outcomes:**

Primary:

Overall survival and progression free survival in patients receiving chemotherapy within and beyond 8 weeks

Secondary:

1. Time frame that constitutes delay in adjuvant chemotherapy leading to worse outcomes.

2. Risk factors for delay in adjuvant chemotherapy

VI. Potential confounders and effect modifiers:

Post operative complications like anastomotic leak, collections etc. that would delay initiation of chemotherapy.

VII**. Data Sources/measurement:**

a. Demographic data – Age , Gender, Comorbidities

Comorbidities: Presence of any comorbidities (44).

b. TNM stage at diagnosis: I , II, III, IV, unknown

c. Pathological staging: 0, I, II, III, IV

d. Margins : Positive, Negative

e. Type of operation: LAR, APE, Laparoscopic /open

f. Radiation: Preoperative, Postoperative , unknown

g. Complications: I, II, III, IV, V Based on Clavien Dindo Classification

h. Re operation : Yes/ No

i. Length of hospital stay : <4 , 4-7, >= 8 days

j. Outcome at discharge

k. First cycle of chemotherapy <8 weeks/ > 8weeks after operation

l. Completed chemotherapy: yes/no

m. Last follow up in hospital

VIII**. Bias:** This is a retrospective and part prospective study. Inherent bias cannot be excluded.

IX. Sample size:

Based on 5 year survival data from a recent study,

$n = 2p'q'/d^2$

Where $p' = p1 + p2/2$

q’ = 100 – p’ d = p2 – p1

p1 = cumulative risk at 5 years among exposed (chemotherapy >8 weeks)

p2 = cumulative risk at 5 years among unexposed (chemotherapy < 8 weeks)

p1= 45

p2=15

n= 2 x 30 x 70 (1.96 + o.84)^2/ 30 x 30

Sample size = 38 cases each exposed (received chemotherapy <= 8 weeks of surgery)

and unexposed (received chemotherapy a > 8 weeks of surgery).

X**. Quantitative variables:**

A univariate analysis will be done to measure the association between each of the risk

factors and the delay in chemotherapy. Adjustments for confounders/ missing data

will be done based on Cox Proportionate Hazard Model

XI. **Statistical methods:**

Overall survival, disease-free survival - defined as the intervals from surgery to death,

disease relapse, respectively. The survival mean or median will be computed using the Kaplan- Meier method and the comparison of the survival outcomes between groups With different variables will be done using Tarone Ware test. Cox regression analysis with stepwise selection will be used to determine the independent prognostic factors for the outcomes after having checked for the proportional hazard assumption. Statistical significance will be calculated at the 95% confidence interval ($p<0.05$), and all analyses was performed using SPSS version 17.

Confidentiality of study participant information

Participant information will be collected in pre-designed data abstraction forms and the investigators shall ensure that strict confidentiality of participant information is maintained at all times. All patient identifiers will be removed during analysis and publication. Only the investigators and the guide shall have access to patient information needed to prepare the planned manuscript under conditions that appropriately protect patient confidentiality.

Results

Demographic characteristics of study population:

A total of 88 patients were included in this study based on the inclusion criteria. All these patients had curative rectal resections(Anterior resection, Low anterior resection, Abdominoperineal excision, Hartmann's procedure, Coloanal anastomosis, Intersphincteric resection). All patients received neoadjuvant radiation to the pelvis with concurrent chemotherapy (LCCRT/ SCRT). All the patients received adjuvant chemotherapy. Among the recruited subjects 50 received adjuvant chemotherapy **within 8 weeks of operation (group 1)** and 38 subjects received adjuvant chemotherapy **after 8 weeks of operation (group 2)**. The demographic characteristics of the patients along with their treatment details are entered in the proforma and analysed. The primary outcome of the study was to look at the survival and disease free survival at 5 years in the two arms.

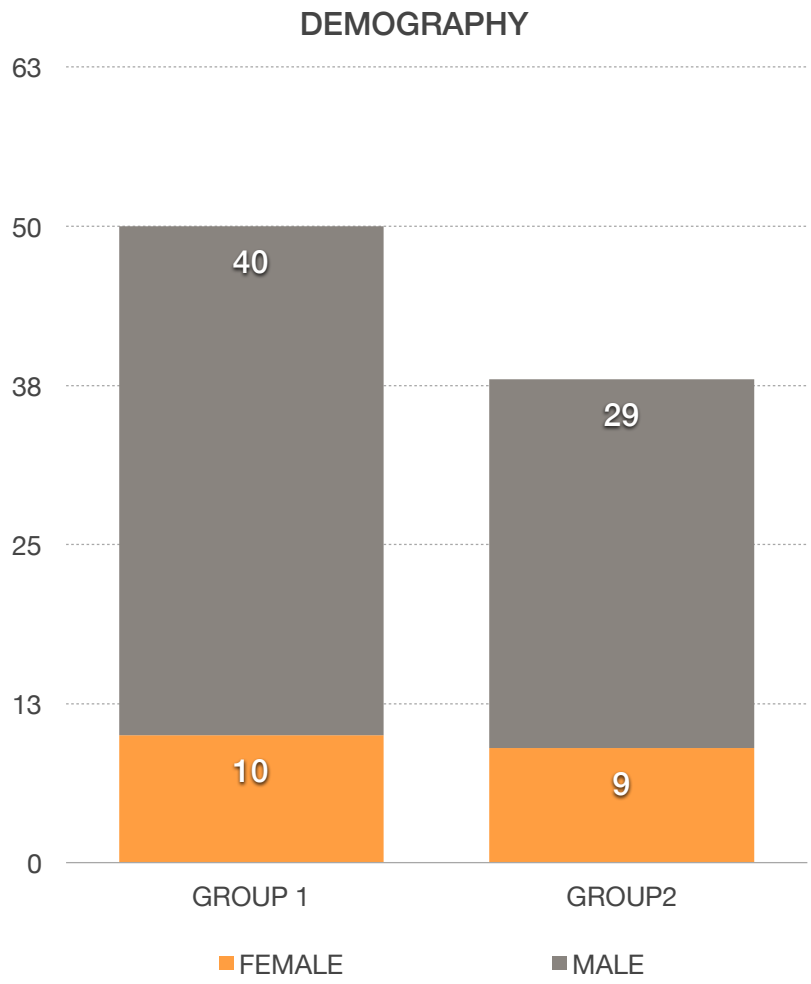
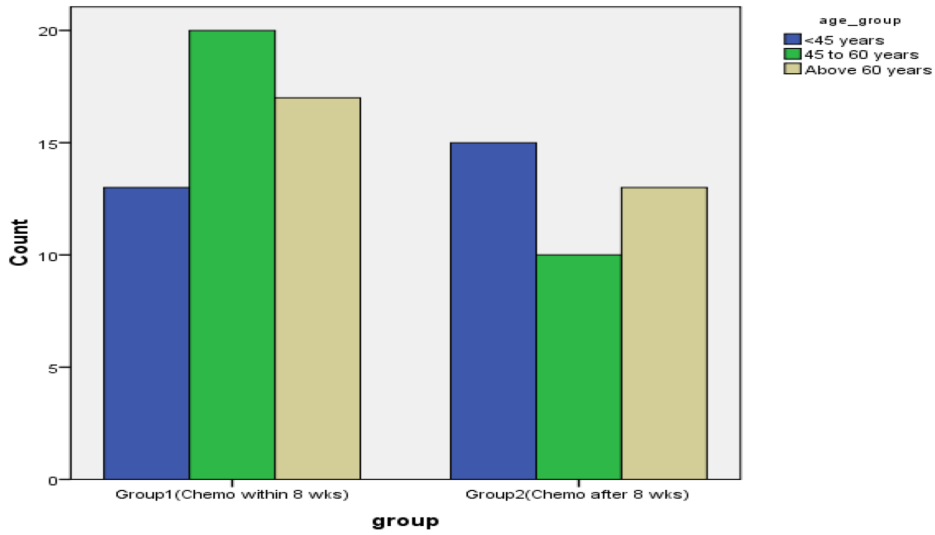


Figure 13 Gender distribution across group 1 and group 2

In the gender distribution, group 1 had 80 % (n = 40) males as compared to 77% (n = 29) in group 2. Distribution of females in group 1 was 20 % (n = 10) and group 2 was 23% (n = 9). Rectal cancers were seen commonly in men in our study population.

A



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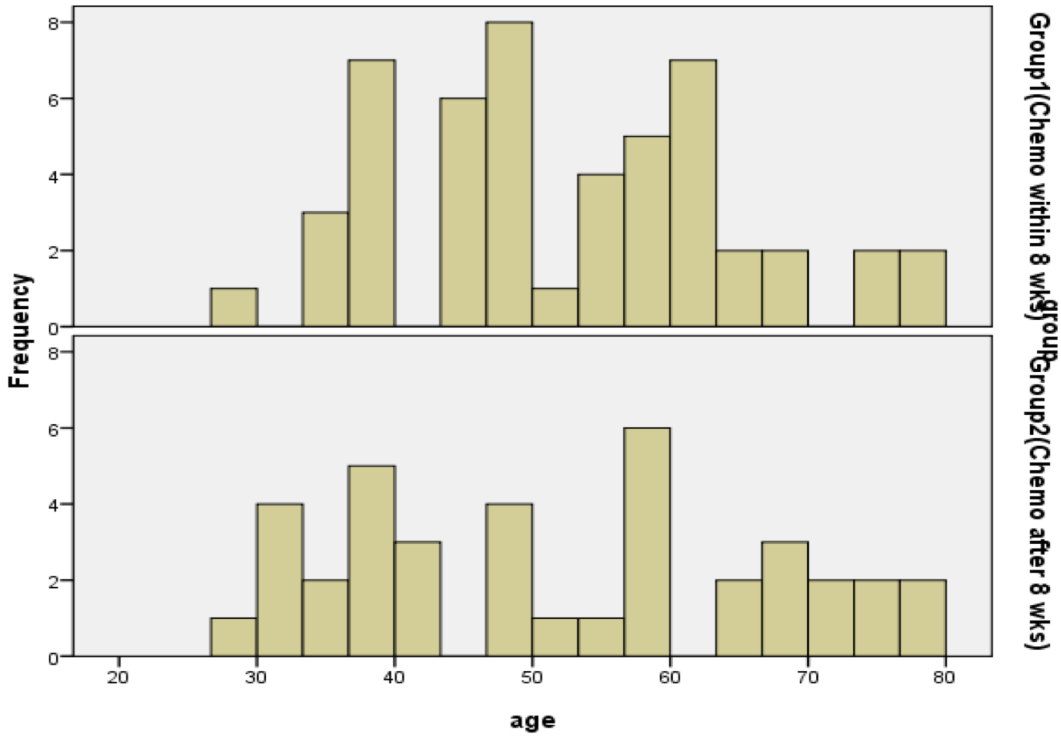


Figure 14 A. Age wise distribution in group 1 and 2, Fig. 14 B All subjects in different age groups

Minimum age of the subjects in the study was 27 years and maximum age was 80 years.

There was equal age distribution in the two groups.

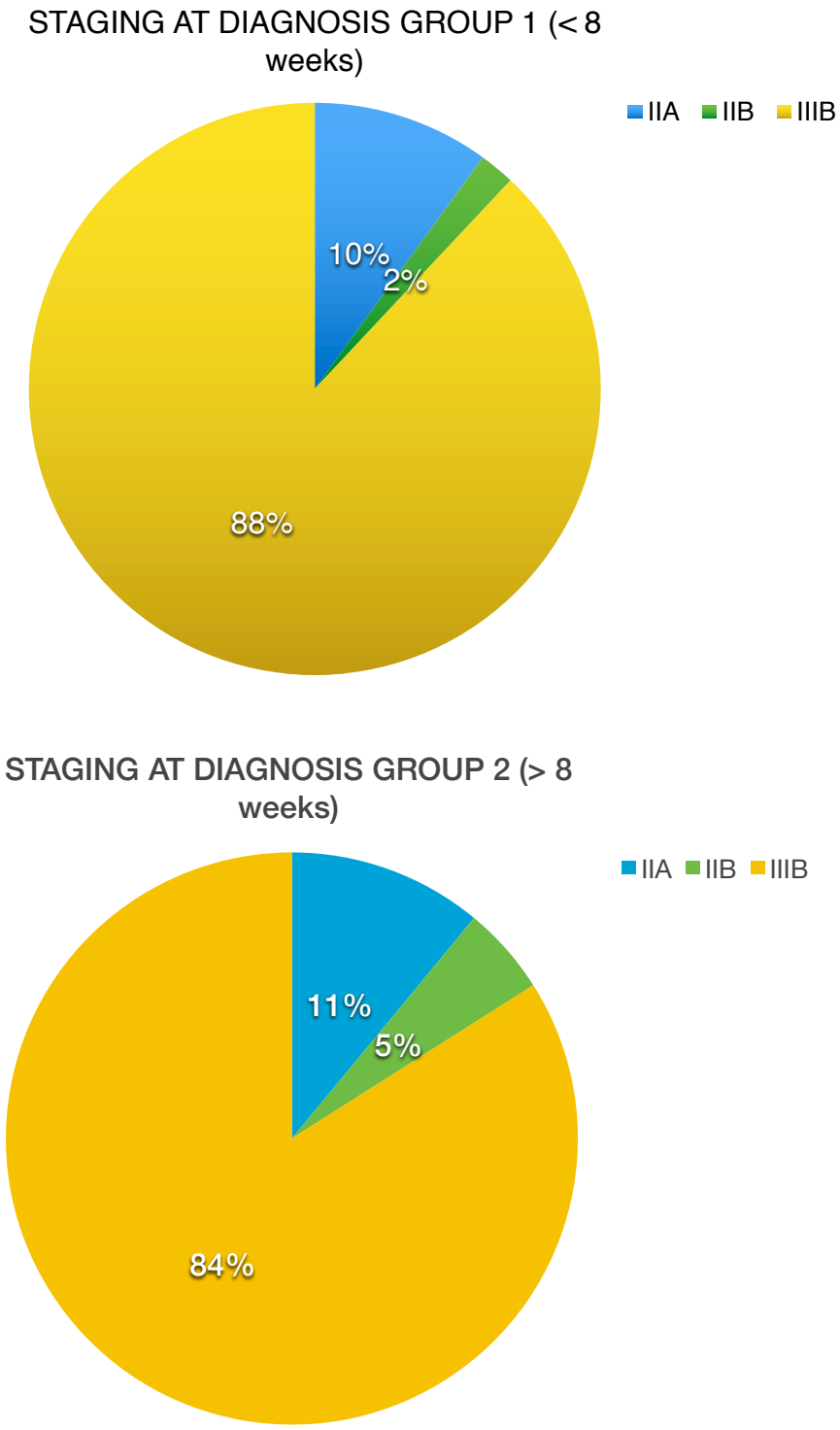


Figure 15 TNM staging at diagnosis

At diagnosis, majority of the patients were diagnosed to have stage III disease (85%).

MRI was done for 99% patients in both groups. 15% of the patients had stage II disease.

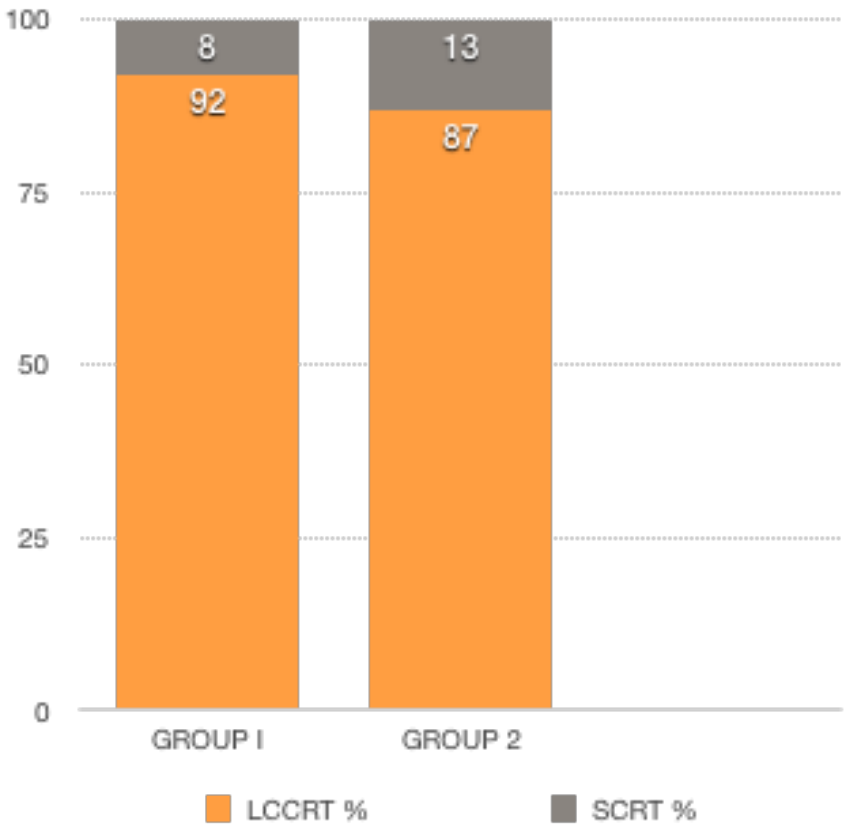


Figure 16 Neoadjuvant radiation therapy with concurrent chemotherapy in two groups

LCCRT – Long course chemoradiotherapy, SCRT – Short course radiotherapy

100% patients in both groups received neoadjuvant chemoradiation in both the groups.

In group 1, 92% patients received long course chemoradiation therapy whereas 8% patients received short course RT. In group 2, 87% patients received long course chemoradiation therapy and 13% received short course RT.

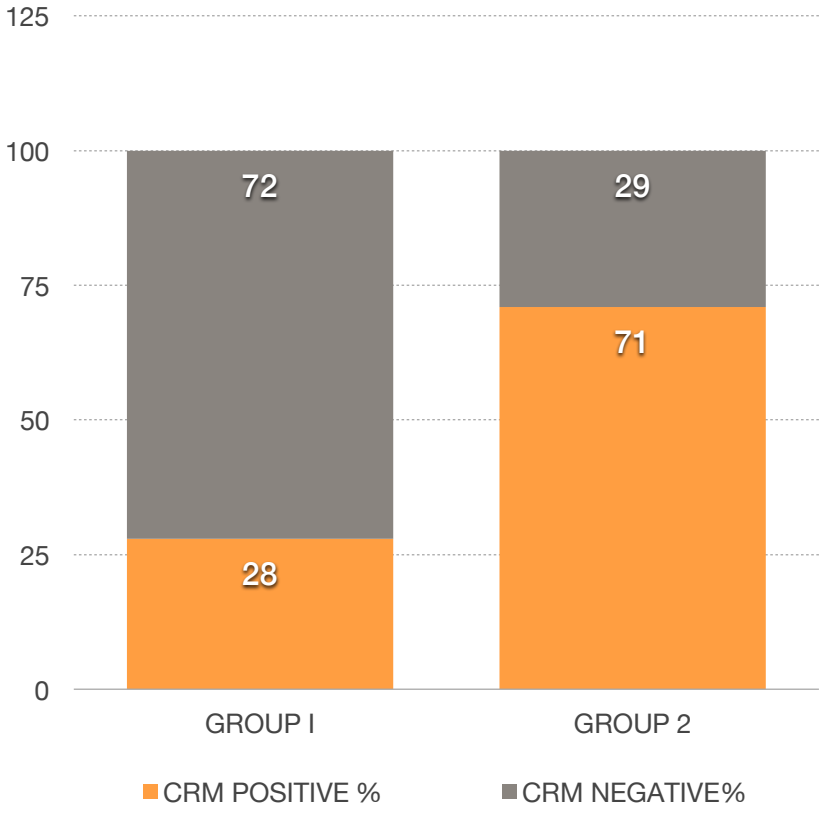


Figure 17 Circumferential resection margin in the two groups

In group 1, 72% of the patients had CRM negative on the final histopathology. In group 2 only 29% patients had CRM negative as compared with 61% patients CRM positive.

The radial margin was involved in majority of group 2 patients.

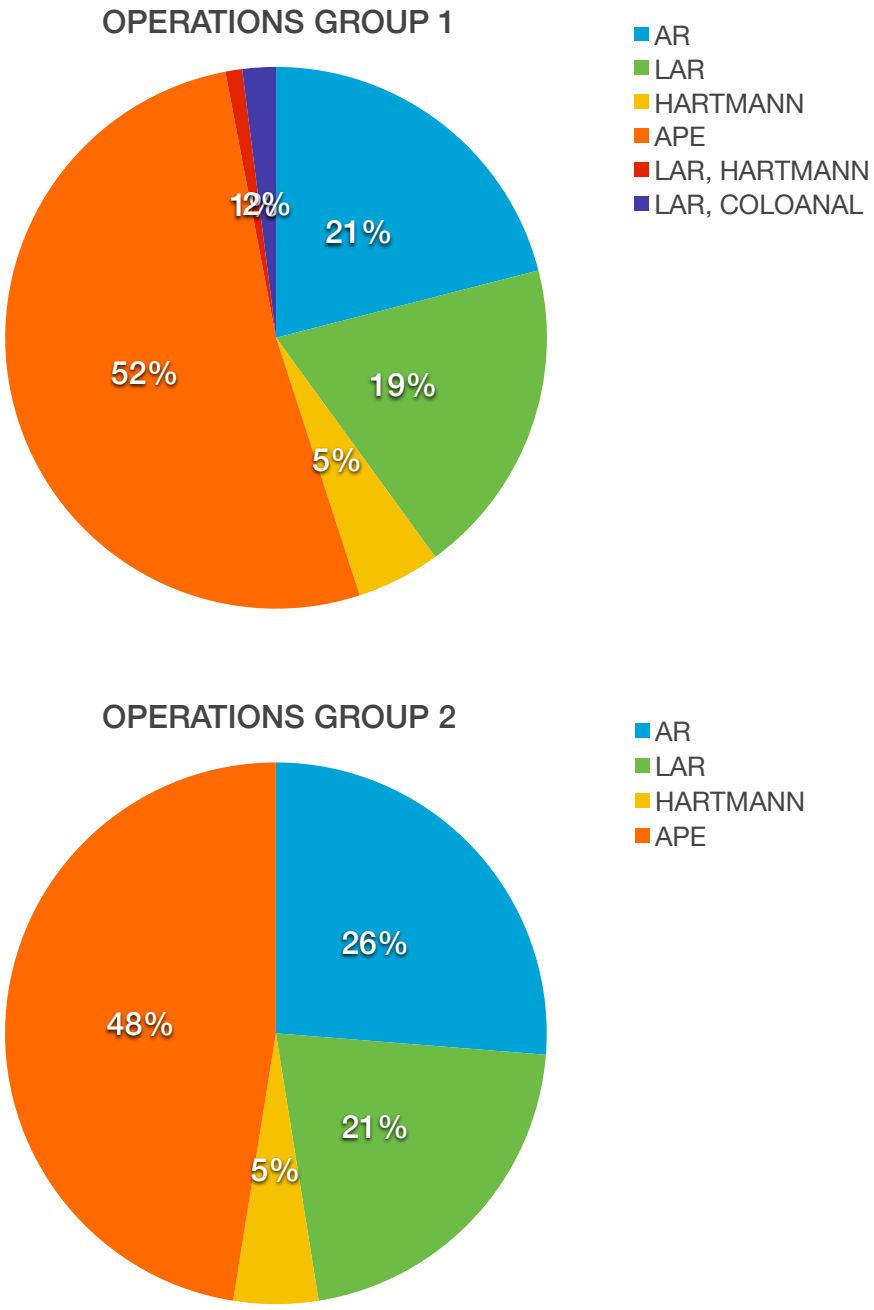


Figure 18 Operative procedure performed in group 1 and 2

Abdominoperineal resection was the commonest operation performed in both groups, 52% in group 1 and 47% in group 2.

Anterior and low anterior resections were the next common.

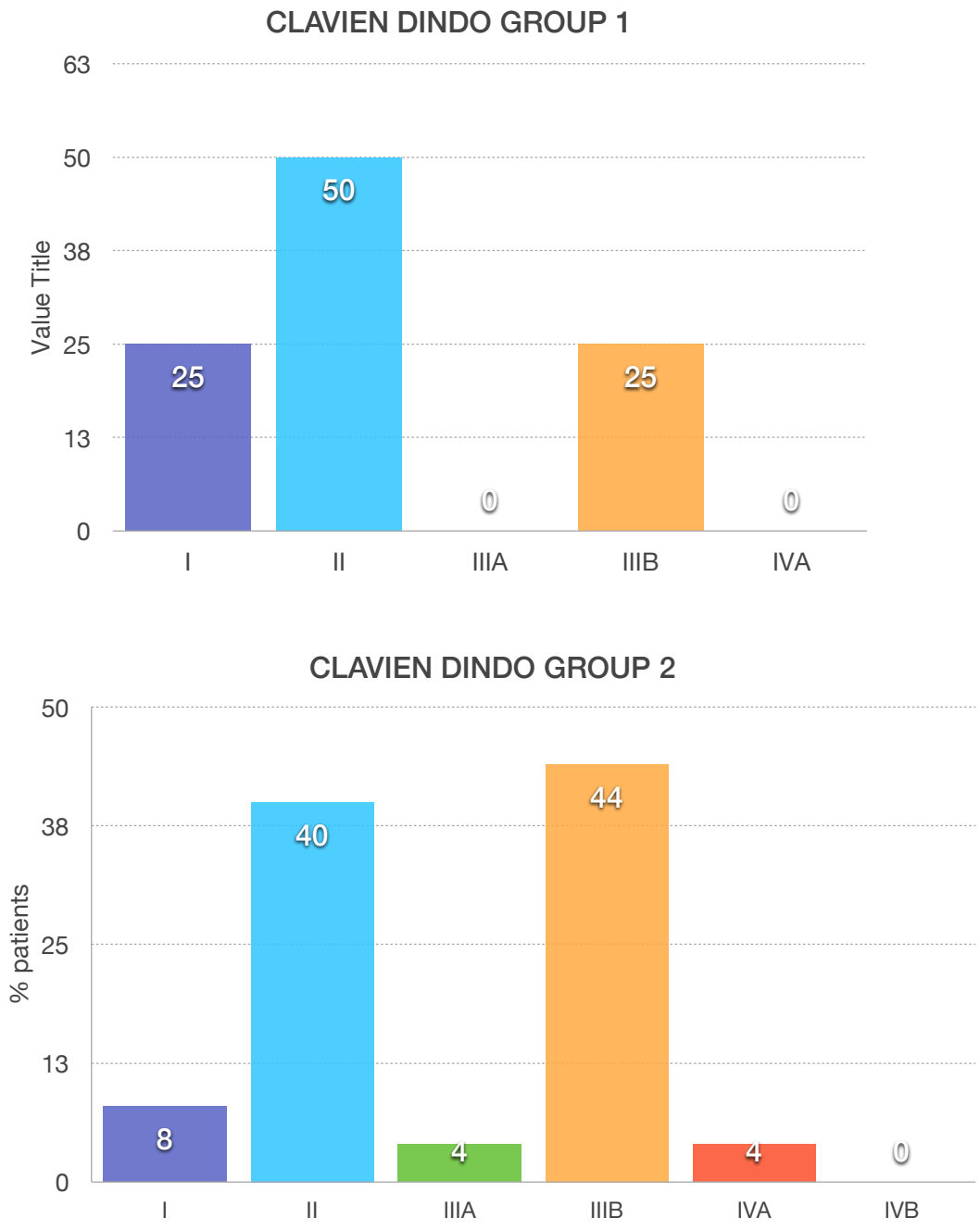


Figure 19 Postoperative complications in the two groups based on Clavien Dindo classification

50% patients in group 1 and 40% patients group 2 had Clavien Dindo classification 2 complications. These complications were superficial surgical site infection, urinary tract

infection and catheter related fever which required antibiotics and prolonged the hospital stay. 44% patients in group 2 and 25% in group 1 required an intervention under anaesthesia for a post operative complication.

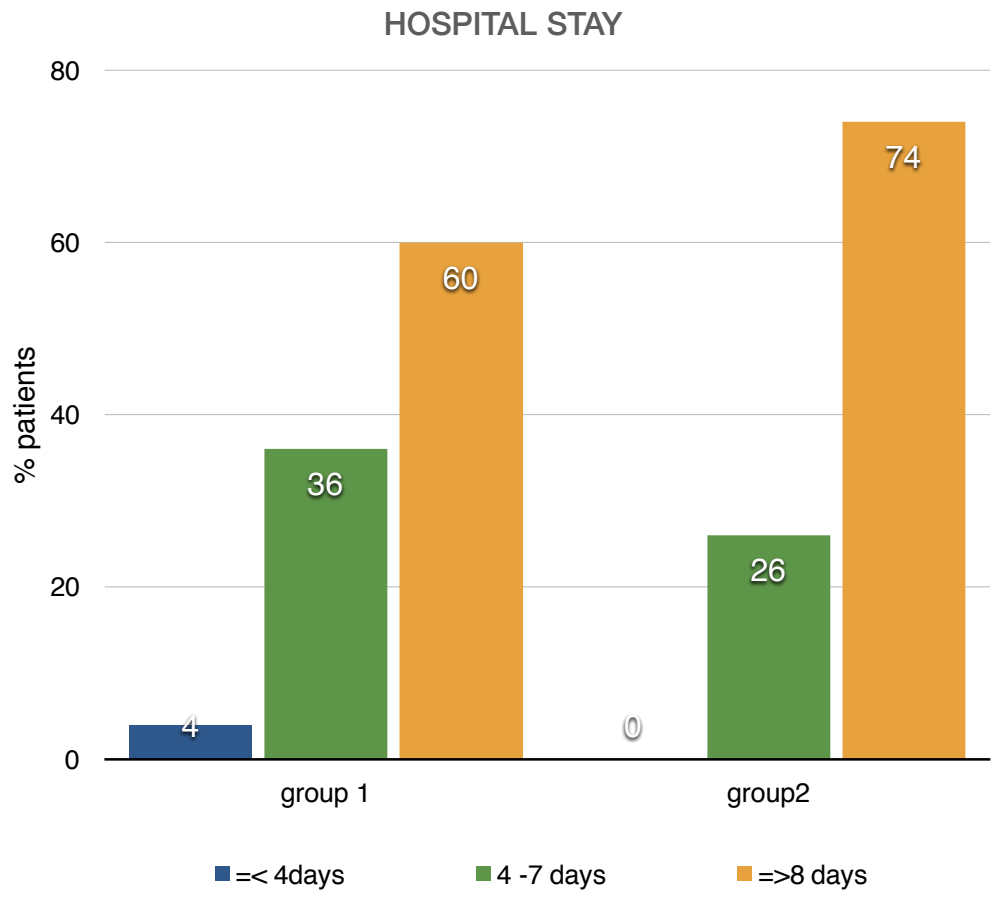


Figure 20 Duration of hospital stay in the two groups post operatively

74% of patients in group 2 had a hospital stay of more than 8 days. and 26% patients had hospital stay 4 -7 days. In group 1, 36 % patients stayed in hospital 4 -7 days, 60%

stayed beyond 8 days and 4 % were discharged within 4 days of operation.

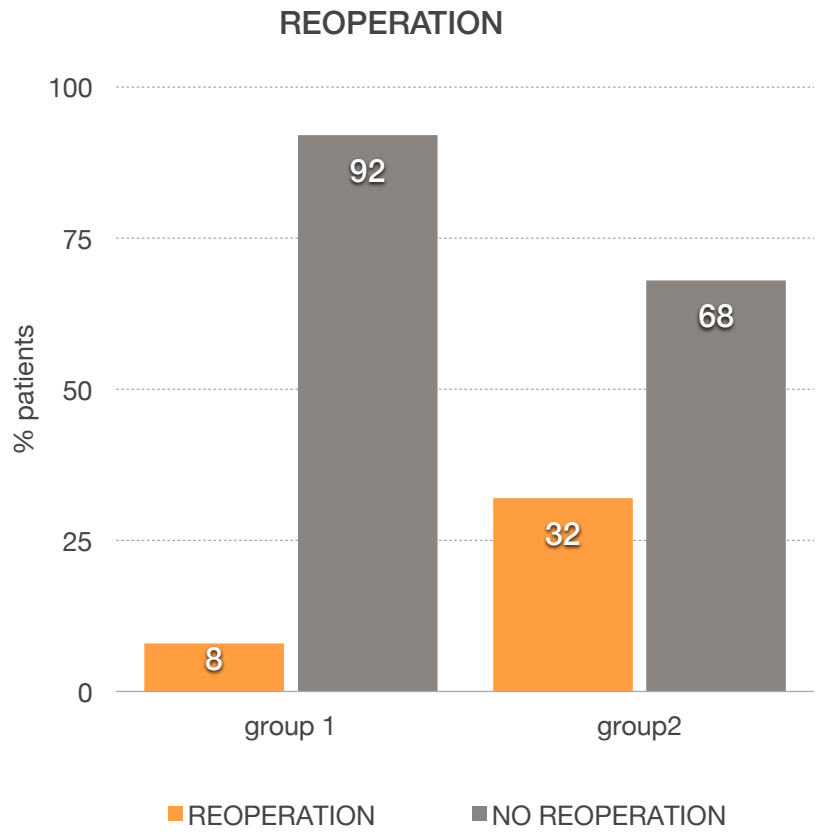


Figure 21 Patients in group 1 and 2 requiring reoperation

Only 8% of patients in group 1 underwent a surgical procedure for a complication whereas 68% of patients in group 2 underwent a surgical procedure post rectal resection.

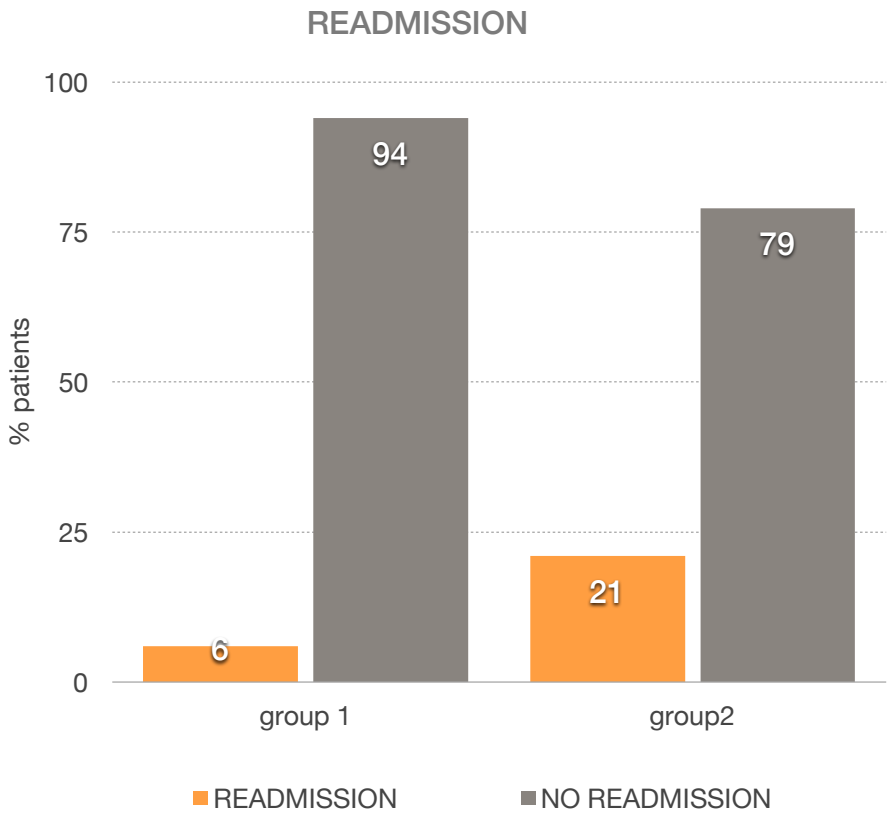
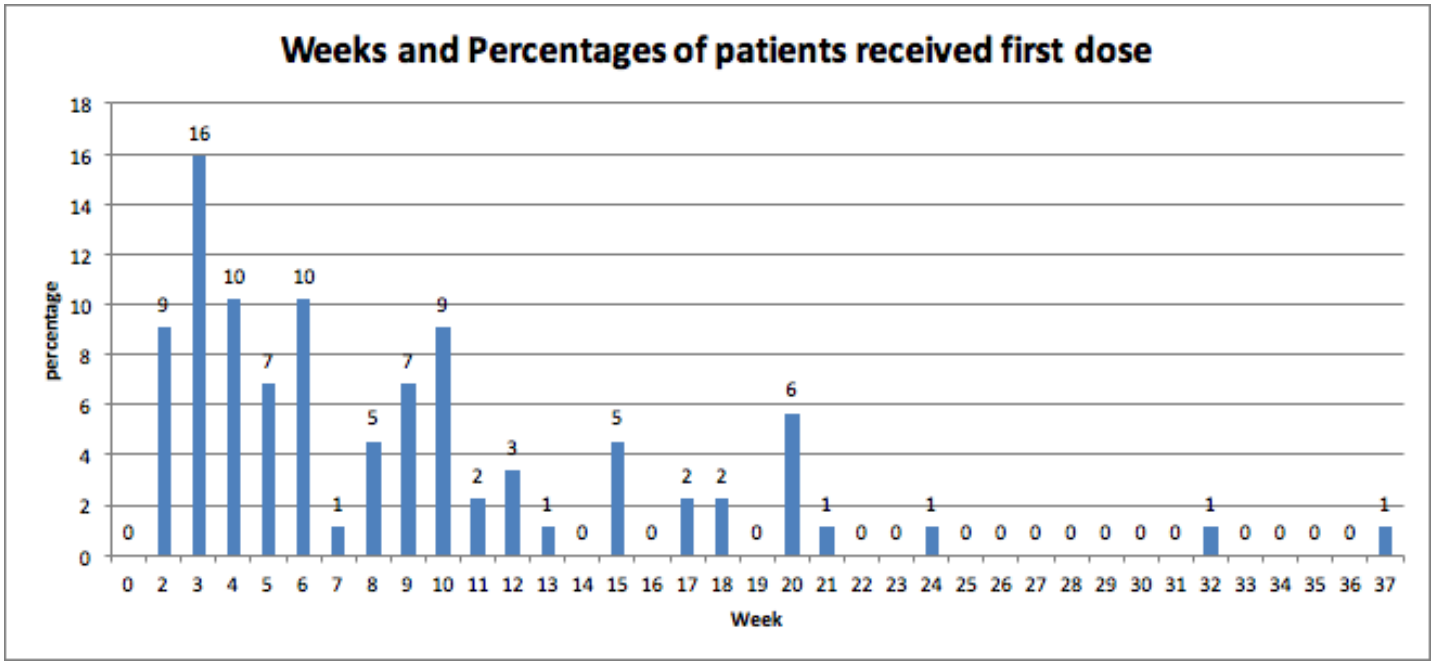


Figure 22 Patients in Group 1 and 2 requiring readmission

Group 2 had 21% readmissions as compared with 6% readmissions in group 1.



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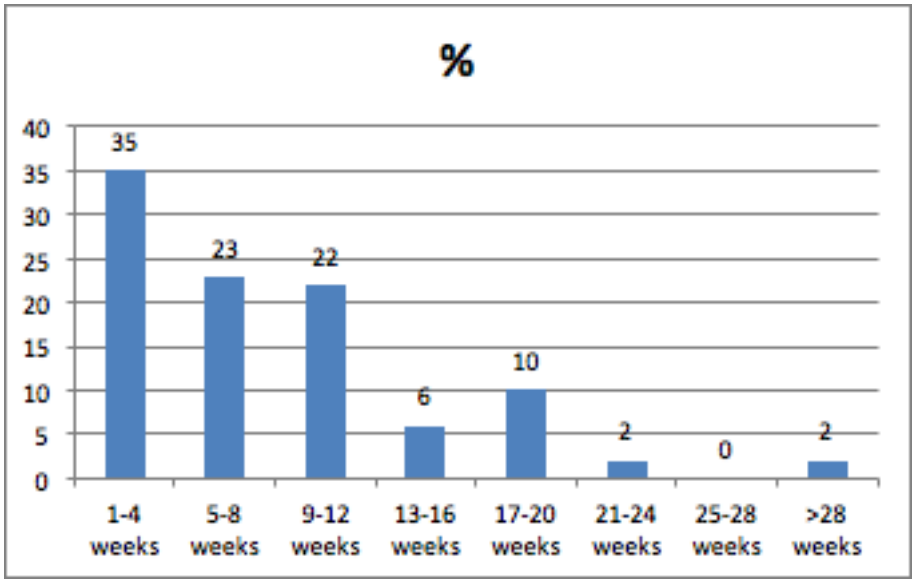

B

Figure 23 Graph A and B, depicting the first dose of chemotherapy after operation in both groups

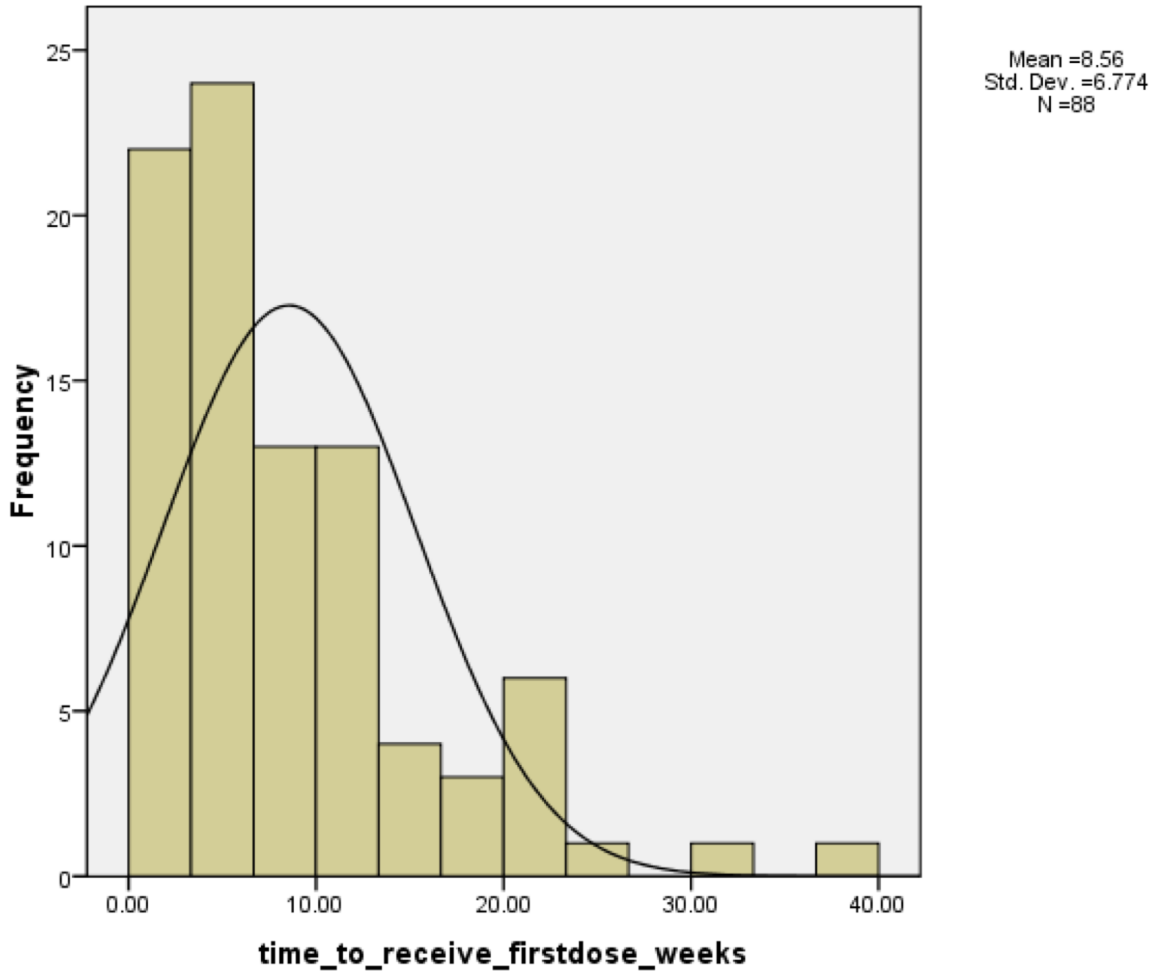

Figure 24 Nomogram for time to receive first dose of adjuvant chemotherapy

The above nomogram shows the time period in weeks of all the subjects in the study. The median(range) week is 6(2-37) for receiving the first dose. That is 50% of the subjects received the first dose within 6 weeks. 25% of the subjects received the first dose within 3 weeks and 75% of the subjects received the chemotherapy within 11 weeks.

Months	Overall disease free survival rate(SE)	Group1 disease free survival rate(SE)	Group 2 disease free survival rate(SE)
12	69.8%(0.052)	71.6(0.070)	67.5(0.077)
24	65.4%(0.055)	66.5(0.074)	64.1(0.081)
60	50.3%(0.062)	45.0(0.086)	0.57

Table 1 Comparing the disease free survival at 1, 2 and 5 years in the two groups.

There was no significant difference noted in survival at 3 and 5 years among the subjects who received adjuvant chemotherapy within and after 8 weeks of rectal cancer resection.

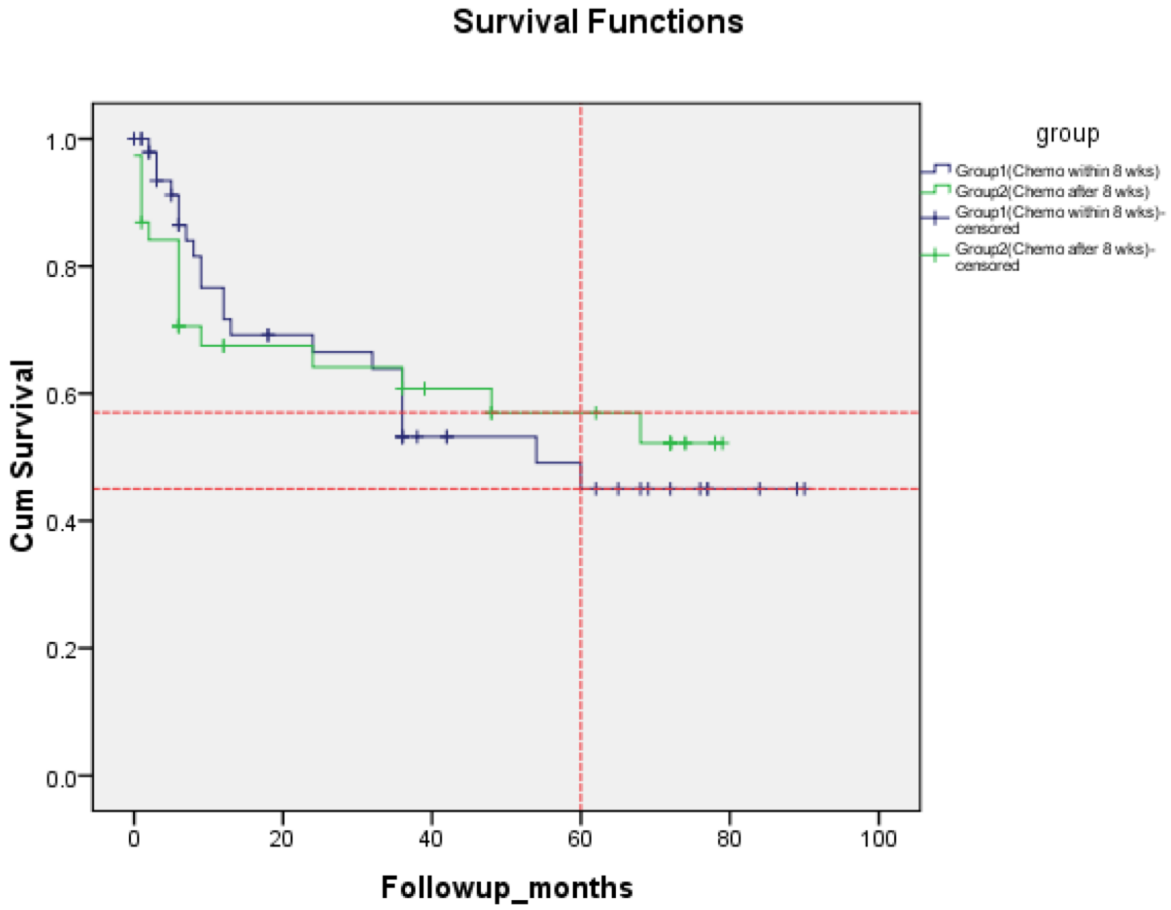

Figure 25 Kaplan Meier curve showing the 5 year survival in subjects in the two groups

Kaplan Meier curve showing no significant difference in the survival in the two

groups.

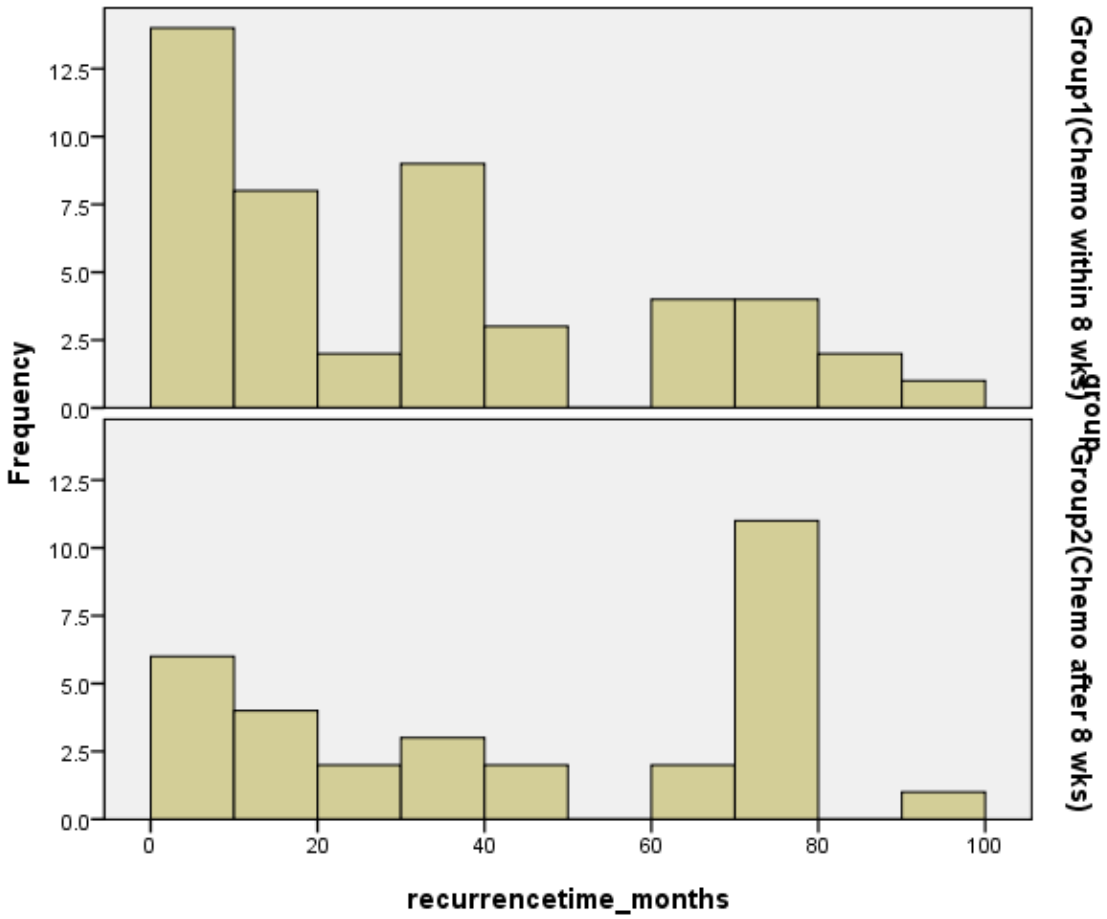

Figure 26 Time to recurrence in months in group 1 and 2

In group 1 recurrence or relapse is seen earlier as the follow of the patients is good.

Where as in group 2 most patients have relapse by 5 years or have lost to follow up by then.

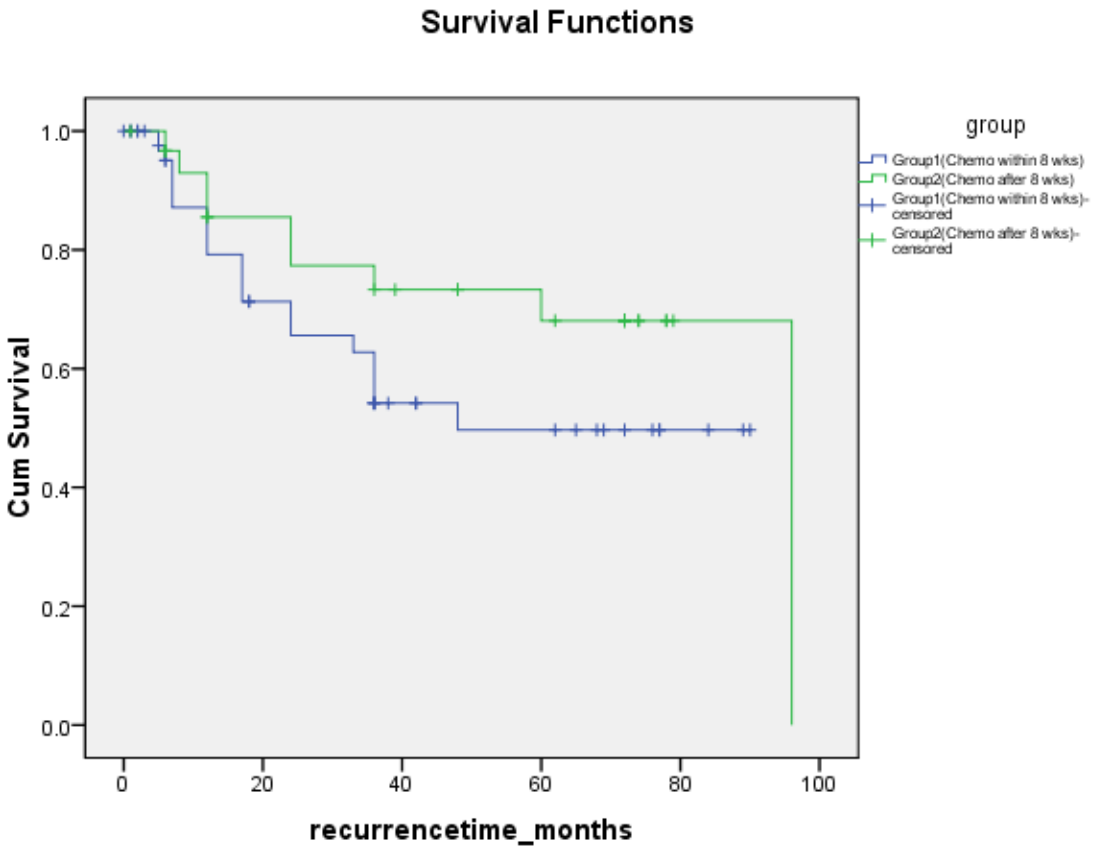

Figure 27 Kaplan Meier curve showing survival functions based on time to recurrence

Both groups had recurrences over varied time frames. In group 1 recurrence was picked up early due to good follow up. Where as, in group 2 majority of recurrences were picked up around 3 and 5 years.

Discussion and conclusions

In our analysis, the majority of patients with stage III rectal cancer had initiated adjuvant chemotherapy within 11 weeks after the date of their surgery. We observed that patients with abdominoperineal resection had perineal wound infection and dehiscence leading to delayed hospital stay. Mostly delay in chemotherapy initiation was due to prolonged hospital stay secondary to post operative complication. The follow up was better in patients who received chemotherapy within 8 weeks of operation. These patients had a longer follow up than the second group. Early recurrences were picked up in patients who received chemotherapy early after resection as their follow up was better. Comorbidities, age and pathological staging did not cause delay in treatment. Even when those factors were taken into account, treatment delay was associated with poorer cancer-specific and overall survival. However, the initiation of chemotherapy within 8 weeks after surgery was not associated with better outcomes. There was no significant difference in overall and disease free survival based on timing of adjuvant chemotherapy.

Limitations

This study was an observational study with prospective and retrospective components.

The patients in the prospective component were consented and enrolled into the study.

Majority of the cases in this study was from the retrospective component. The data

was obtained from the inpatient and outpatient case sheets which was available in the

medical records

department. The inpatient and outpatient case sheets for some patients were not

complete and it had missing records. In the prospective arm the data collection was

complete and there was no missing data.

The number of cases in this study was small to make a comparison.

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44. ***Postoperative complications in rectal cancer patients are associated with delays in chemotherapy which lead to worse disease free and overall survival Rectal cancer complications chemotherapy Sarah E. Tevis, MD,1 Brittney M. Kohlnhofer, BS,2 Sarah Stringfield, MD,2 Eugene F. Foley, MD, FACS,1 Bruce A. Harms, MD, FACS,1 Charles P. Heise, MD, FACS,1 and Gregory D. Kennedy, MD, PhD, FACS1.***

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ANNEXURES

A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy

DATA EXTRACTION SHEET:

Study ID:

Name: Age: Sex: Male / Female

Hospital No.: Contact number: Address:

1. Co-morbidities:

Diabetes mellitus	Smoking	COPD	Hypertension	Acute renal failure
Steroid/ immunosuppressive therapy	Body weight loss> 10% in last 6 months preoperatively	Bleeding disorder	Blood transfusion 72 hours prior to surgery	Sepsis 48 hours prior to surgery

2. TNM staging at diagnosis: Stage grouping

I	II	III	IV	Unknown

T	Tx	T0	T1	T2	T3	T4a	T4b
N	Nx	N0	N1a	N1b	N1c	N2a	N2b
M	Mx	M0	M1a		M1b		
Based on:							
	CT	MRI	Ultrasonography		Bone scan	X ray	
Region							

3. Pathological staging:

0	I	II	III	IV

A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy

T	Tx	T0	T1	T2	T3	T4a	T4b
N	Nx	N0	N1a	N1b	N1c	N2a	N2b
M	Mx	M0	M1a		M1b		

4. Circumferential Resection Margins: Positive/ Negative

5. Type of operation :

	Open	Laparoscopic
Anterior resection		
Low anterior resection		
Hartmann's		
Intersphincteric resection		
Coloanal anastomosis		
Abdominoperineal excision		

6. Radiation and chemotherapy

Radiation	Yes/ No	Duration in weeks	Fractions	Total Dose
	Preoperative			
	Postoperative			
LCCRT/ SCRT				
Concurrent chemotherapy	Yes/ No	Regimen	Duration in weeks	Cycles
Preoperative chemotherapy	Yes /No			

A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy

7. Complications:

Clavien Dindo	I	II	III A	IV A	V
			III B	IV B	
Complication:					

8. Reoperation : Yes/ No

Indication	

9. Length of hospital stay: (post operative hospital stay)

Exact number of days:

Days	<4	4 - 7	=> 8

10. Readmission: Yes/ No

11. First cycle adjuvant chemotherapy:

Exact number of weeks from the operation to first cycle of chemotherapy:

Weeks after operation	< 8	> 8

12. Completed adjuvant chemotherapy: Yes/ No/ Unknown

Chemotherapy regimen :

13. Last follow up in Hospital:
Whichever is applicable -
Exact number of months: Exact number of years:

Years after treatment completion	=< 2	3 - 5	>5

A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy

14. Current status

Disease free	Recurrence	Dead
Living with disease	Time to recurrence	Date of death

A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy

PATIENT INFORMATION SHEET

You are being requested to participate in a study involving patients with rectal cancer. Please read/ listen to this information form carefully. Take time to ask as many questions as you want. The study personnel will explain any word or information you do not clearly understand.

DESCRIPTION OF THE STUDY: Rectal cancer is the third most common cancer in the world. This disease is usually treated with radiation therapy followed by an operation. After the operation, chemotherapy is administered to some patients for a better outcome. The purpose of this study is to find out the reasons for delay in starting of chemotherapy, if any, and the effect of delay on the ultimate outcome.. Approximately 100 patients with rectal cancer requiring such adjuvant chemotherapy will be enrolled for this study.

FORESEEABLE RISKS OR INCONVENIENCES: No risks or inconveniences are expected to you by participating in this study. You will not be required to pay any money at any stage for the study.

REASONABLY EXPECTED BENEFITS: The result of the study will be of use for patients undergoing treatment for rectal cancer in the future. You will not be given any financial or 'in kind' rewards for participating in this study.

STUDY PARTICIPATION AND WITHDRAWAL : Refusal to participate or study discontinuation will not result in any penalty, or compromise of your medical care, or loss of benefits.

DATA COLLECTED: If you consent to participate in this study, the study personnel will collect the following information about you: demographic data, a history of your illness, course in hospital, last hospital visit, present condition.

CONFIDENTIALITY OF YOUR INFORMATION: Your personal data will remain strictly confidential. Only the study doctors will be able to match your data to your identity. If the results of this study are published, you will not be identified by name in any publication or presentation of results.

FURTHER INFORMATION:
In addition to this information consent document, you may ask for additional information, from:
Dr. Farheen Khan
Dept. of General Surgery 2, CMC Hospital, Vellore – 632004
Phone: 0416 – 2282159
E-mail: farheen1234@gmail.com

A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy

INFORMED CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Hospital Number	Study ID	Participant's Name	Age

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Name of the study participant / signatory:

_____

Signature / Thumb impression:

Investigator

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD
CHRISTIANMEDICALCOLLEGE,
BAGAYAM, VELLORE 632002, TAMIL NADU, INDIA

Ref: FG/9099/10/2014

January 31, 2015

Mr. Robby Pria Sundersingh
The Treasurer
Christian Medical College,
Vellore.

Dear Mr. Robby Pria Sundersingh,

Sub: **Fluid Research Grant Project:**
A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy.
Dr. Farheen Khan, PG Registrar, Dr. Mark Ranjan Jesudason, Dr. Benjamin Perakath, Dr. Rohin Mittal, Surgery unit 2, CMC, Vellore.

Ref: IRB Min. No. 9099 dated 06.10.2014

The Institutional Review Board at its meeting held on October 6th 2014 vide IRB Min. No. **9099** accepted the project for *5,000/- INR (Rupees Five Thousand only) will be granted for 2 years. If overspent the excess should be debited form the respective departmental or Special funds.* Kindly arrange to transfer the sanctioned amount to a separate account to be operated by Dr. Farheen Khan (farheen1234@gmail.com) and Dr. Mark Ranjan Jesudason (ranjanbernice@cmcvellore.ac.in)

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD, MNAMS, DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

CC: Dr. Farheen Khan, Surgery, CMC, Vellore
Dr. Mark Ranjan Jesudason, Surgery, CMC, Vellore.
File

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

October 14th, 2014

Dr. Farheen Khan
PG Registrar
Department of General Surgery
Christian Medical College
Vellore 632 004

Sub: **Fluid Research Grant NEW PROPOSAL:**
A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy.
Dr. Farheen Khan (EmploymentNumber:29374) , PG Registrar, GeneralSurgery, Dr. Mark RanjanJesudason, (Employment Number:28081) surgery unit 2, Dr. BenjaminPerakath (Employment Number: 03758), surgery Unit 2 Dr. Rohin Mittal (EmploymentNumber: 28639), surgeryunit2

Ref: IRB Min No: 9099 dated 06.10.2014

Dear Dr. Farheen Khan,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project title "A study on the effects of delay in adjuvant chemotherapy on survival in patients undergoing curative resection for rectal cancer and the risk factors associated with delay in chemotherapy." on October 6th, 2014. I am quoting below the minutes of the meeting.

The Committee raised the following queries:

1. Necessity of chemoradiation before may be a confounder. Perhaps, exclude patients who do not have chemoradiation be excluded from the study.
2. Record the number of weeks inclusive for therapy.
3. Remove the term: "Sponsor for the study".
4. Include a radiation oncologist as a coinvestigator.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Farheen Khan and Dr. Mark RanjanJesudason were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members. After discussion, it was resolved to**ACCEPT the proposal AFTER receiving the suggested modifications and answers to the queries.**

Note:
1. Kindly **HIGHLIGHT** the modifications in the revised proposal.
2. Keep a **covering letter and point out the answer to the queries**.
3. Reply to the queries should be submitted within **3 months** duration from the time of the thesis/ protocol presentation, if not the thesis/protocol have to be resubmitted to the IRB.
4. The **checklist** has to be sent along with the responses.

Email the details to research@cmcvellore.ac.in and send a hard copy through internal dispatch to Dr. Nihal Thomas, Addl. Vice-Principal (Research), Principal's Office, CMC.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

CHRISTIAN MEDICAL COLLEGE VELLORE INDIA

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

CC: Dr. Mark RanjanJesudasan, General Surgery, CMC

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